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(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

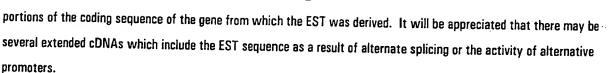
Background of the Invention

The estimated 50,000·100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.
Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mischaracterized as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include



In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- α , interferon- β , interferon- γ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

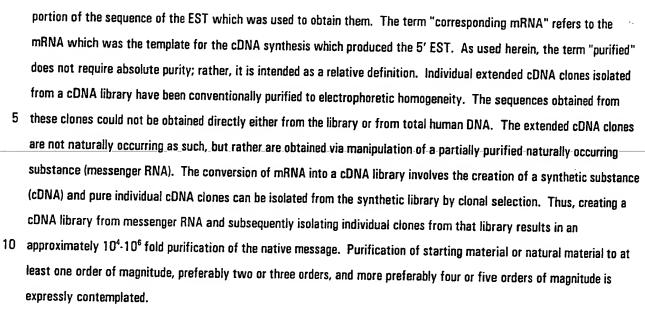
5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5^{\prime} coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a



As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone

20 molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

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cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.



In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired
proteins.

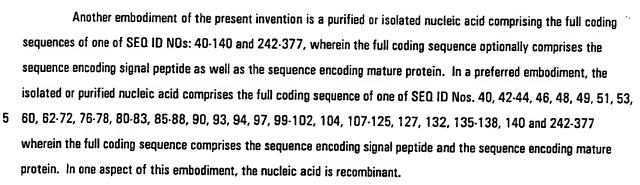
The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID Nos: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.



A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

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amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

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40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

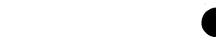
Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.



A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polypuculeotides encoding said polypeptides.

Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and NotI. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

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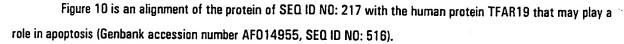


Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

Detailed Description of the Preferred Embodiment

15 I. Obtaining 5' ESTs

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The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'. triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

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may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μg of RNA was incubated in a final reaction medium of 10 μl in the presence of 5 U of T_4 phage RNA ligase in the buffer provided by the manufacturer (Gibco \cdot BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μl of 32 pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH₄, NaBH₃CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

EXAMPLE 2

Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

- 0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step. Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:
 - + Cap:
- 25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)
 - -Cap:
 - 5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID ND:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE 3

Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

- Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.
 - Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with 32 pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with 32 pCp as described in Example 1.
 - Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.



The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 · 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

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Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with ³²pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula $H_2N(R1)NH_2$ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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EXAMPLE 8

Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100μ l of 0.1N sodium hydroxide, 1.5 μ g mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.





Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 μl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 μg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO₄/acetone. The pellet was resuspended in 200 μl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO₄/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).



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10 μ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 μ l of 10 mM urea and 2 μ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 μ m.

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The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with ³²P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)

GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEO ID NO:6)

dehydrogenase



3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
 - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the 20 presence of cDNA.
 - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
 - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
 - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEO ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA



ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first
and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572
and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards,
supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a
Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art
using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold
Spring Harbor Laboratory Press, 1989.

II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

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Preparation of mRNA

Total human RNAs or PolyA + RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA + RNA was isolated from total RNA (LABIMO) by two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

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Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12. Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto



The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

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Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

25 BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.
Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined
match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn-helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.



Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

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Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENETM database which were derived from undesired sequences such as transfer-RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

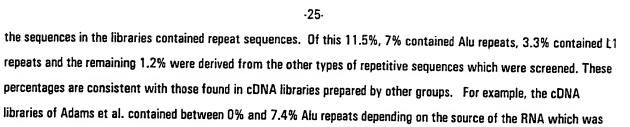
To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNAs. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of



used to prepare the cDNA library (Adams et al., Nature 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of 15 "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE $^{ exttt{TM}}$ database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit lpha and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the 30 corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA



sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENETM was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

-27-EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

EXAMPLE 24

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Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAGTM database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAGTM database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAGTM database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, as described below in Example 25.

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail—30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy



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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

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It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the
serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method,
cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene
expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first
restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least
once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding
to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for
hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the
digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the
cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are 30 obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides.

After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

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Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al. (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., *supra*) or synthesized and then addressed to the chip (Sosnowski et al., *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are
synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino amino acids of the sequences of SEQ ID NOs: 40-140 and



242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEO ID NOs: 40-140 and 242-377.

EXAMPLE 27

General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

10 a) First strand synthesis

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

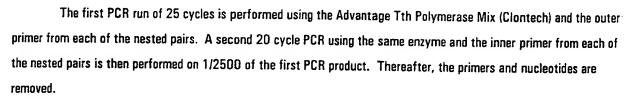
After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, PCR Meth. Appl. 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., Nucleic Acids Res. 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.



5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

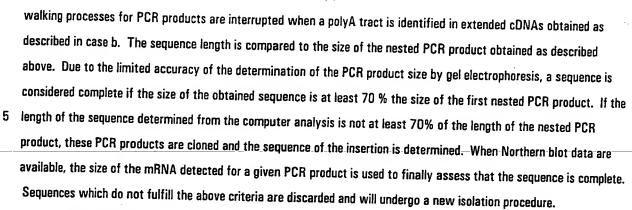
c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

30 primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer



Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, 30 contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA



Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not

a) Elimination of undesired sequences

of interest are searched as follows.

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs





having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungalcontaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of 5 extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 85% or more than 30 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs 10 are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 15 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

20 Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

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have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs

are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E = 0.001.

Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from





alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.



The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or

functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the
members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in
the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at
http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs
(http://ulrec3.unil.ch/ftpserveur/prosite_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

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proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-



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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with $(\cdot[^{32}P]ATP$ (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can aiso be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X106 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X106 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

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1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

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EXAMPLE 29

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended



cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5%increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

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sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double



stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

EXAMPLE 30

Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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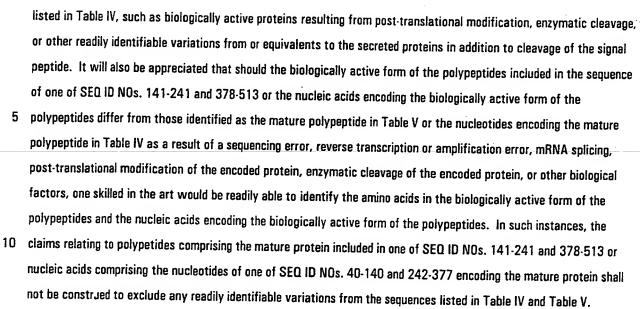
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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEO ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEO ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences



In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEO ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEO ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEO ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-30. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

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The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.



Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro ExpressTM Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

20 <u>Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface</u>

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.



As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in **Current Protocols in Immunology**. J.E. Coligan et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. **Current Protocols in Immunology**., *supra* Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte



Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., **J. Immunol**. 137:3494-3500, 1986; Takai et al.; **J. Immunol**. 140:508-512, 1988; Bertagnolli et al., **J. Immunol**. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models



of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β₂ macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.



pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell linesindicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present 15 invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as





Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle

(smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller 30 et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

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Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,





Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

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Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion



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molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

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EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or



circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

15 receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

20 are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, in vitro transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives in vitro transcription. The resulting pools of mRNAs are introduced into Xenopus laevis oocytes. The oocytes are then assayed for a desired acitivity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

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Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. 5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor



proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended

cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents. The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The 5 antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding 10 fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 15 141-241 and 378-513.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an 20 Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

Monoclonal Antibody Production by Hybridoma Fusion A.

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or 25 derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the 30 -culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.



B. **Polyclonal Antibody Production by Immunization**

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors 5 related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic 20 compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable 25 therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a 30 variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C





ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or



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genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

EXAMPLE 44

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Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

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Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30





nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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EXAMPLE 46

Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The ³²P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).



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Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

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Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and XbaI. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized
with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose
filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of

Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.



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A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: **Basic 503 Clinical Immunology**, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: **Methods in Immunodiagnosis**, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 μ l, and containing from about 1 to 100 μ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome





Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human

Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology: Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a ³²P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIDS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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EXAMPLE 51

Mapping of Extended 5' ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 μ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at



70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra*.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

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10 chromosome.

Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

EXAMPLE 54

Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the





extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

EXAMPLE 55

Use of Extended cDNAs or 5' ESTs to Clone Upstream

Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or ' EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc)₂, and 1 μ l of the Tth polymerase 50X mix in a total volume of 50 μ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 μ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 μ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence. 20

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

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Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.





Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

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EXAMPLE 58

Identification of Proteins Which Interact with Promoter Sequences, Upstream

Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

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to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or

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more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO
92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop"
10 structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10⁻¹⁰M to 1x10⁻⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10⁻⁷ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.



PCT/IB98/02122

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., supra.

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In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with 10 a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also 15 inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide 25 synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as 30 Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide . The cell functions to be monitored are predicted based upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived with known gene sequences that have been associated with a particular function. The cell functions can also be





predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

EXAMPLE 62

Use Of Signal Peptides Encoded By 5' Ests Or Sequences

Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin *et al., J. Biol. Chem.,* **270**: 14225-14258 (1995); Du *et al., J. Peptide Res.,* **51**: 235-243 (1998); Rojas *et al., Nature Biotech.,* **16**: 370-375 (1998)).

When ceii permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.





In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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EXAMPLE 64

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 30–53) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

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The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

15 A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEO ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEO ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,





may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection .

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Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells. 10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10: 685-686 (1994)). The first 15 transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEO ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially 25 associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395 : 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic 30 shock.

Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the



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alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8 : 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

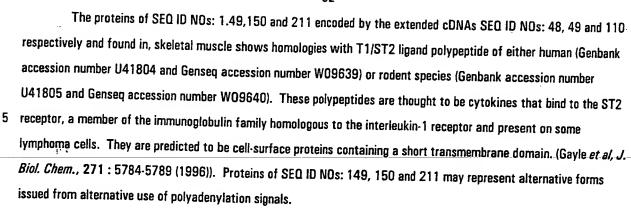
Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi et al, FEBS Lett., 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink et al., Hum. Mol. Gent., 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEO ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions Proteins of SEQ ID NOs: 149, 150 and 211





The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10**:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-l-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,





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hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

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Protein of SEQ ID NO: 163

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The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252:69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369 : 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

Protein of SEO ID NO: 153



The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number 009273) that belongs to the multigene SRE family of C. elegans receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat 5 tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10:685-686 (1994)).

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Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction 10 and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits 15 homology with part of the tRNA pseudouridine 55 synthase found in Escherichia Coli (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

Protein of SEQ ED NO: 240

The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 30 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

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inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

.95.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several



types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

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Protein of SEQ ED NO: 167

The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

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Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

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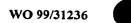
As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a





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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.



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SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name





TABLE I

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	TABLE	
SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	41
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52	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
53	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
54	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
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55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
56	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
61	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
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76 77 78	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997 U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998 U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	136 75
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80	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	130
81	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	65
82	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	54
į.	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	78
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91 L	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	61
92 U	J.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	62
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96 U	J.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	63
97 U	J.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	52
98 U	J.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	62
1	J.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	176
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	.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	64
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TABLE II : Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S-61 X-16	90	17
tRNA	Fasta	both	•	80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S-72	70	40
Repeats	Biastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S-108	90	30
ESTs	Blatsn	both	S-108 X-16	90	30
Proteins	blastxŋ	top	E-0.001		

^{*} use "Quick Fast" Database Scanner

 $[\]perp\,$ alignment further constrained to begin closer than 10bp to EST\5' end

 $^{5 \}quad \eta \quad \text{using BLOSUM62 substitution matrix}$





TABLE III: Parameters used for each step of extended cDNA analysis

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	Search charact	eristics	Selection characteristics				
Step	Program	Strand	Parameters	Identity (%)			
miscellaneous •	FASTA	both	•	90	Length (bp)	Comments	
tRNA*	FASTA	both	 	80	-		
rRNA*	BLASTN	both	S-108	80	90		
mtRNA*	BLASTN	both	S-108	80	40		
Procaryotic ¹	BLASTN	both	S-144	90	40		
Fungal*	BLASTN	both	S-144	90	40		
Alu*	BLASTN	both	S-72		40		
L1'	BLASTN	both	S=72	70	40	max 5 matches, masking	
Repeats*	BLASTN	both	S=72	70	40	max 5 matches, masking	
PolyA	BLAST2N	top	W-6,S-10,E-1000	70	40	masking	
Polyadenylati on signal	·	top	AATAAA allowing 1 mis	90 match	8	in the last 20 nucleotides in the 50 nucleotides preceding the 5' end of th	
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching	
ESTs*	BLAST2N	both		90	20	sequences	
Geneseq	BLASTN	both	W-8, B-10	90	30		
ORF	BLASTP	top	W=8, B=10			on ORF proteins, max 10	
Proteins*	BLASTX	tep	E-0.001	70	30	matches	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters



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TABLE IV

TABLE 14						
ld	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
40	7 through 471	7 through 99	100 through 471	472	537 through 542	554 through 568
41	168 through 332		168 through 332	333	557 through 562	334 11100911 300
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614	·	- 002 tillough 899
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036
46	443 through 619	443 through 589	590 through 619	620	1.	1267 through 1276
47	206 through 747		206 through 747	 		
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	1.	21 through 41	42	328 through 333	
51	35 through 631	35 through 160	161 through 631	632	901 through 906	357 through 370
52	271 through 399	1.	271 through 399	400		979 through 994
53	103 through 252	103 through 213	214 through 252	253		
54	2 through 460	1.	2 through 460	461	712 through 710	588 through 597
55	31 through 231	T	31 through 231	232	713 through 718	735 through 748
56	305 through 565	 	305 through 565	566	769 through 774	690 through 703
57	124 through 873	124 through 378	379 through 873	874	694 through 699	713 through 725
58	135 through 206	1.	135 through 206	207	1673 through 1678	1694 through 1705
59	135 through 818		135 through 818	819	850 through 855	1056 through 1069
60	33 through 290	33 through 92	93 through 290	291	909 through 914	1071 through 1084
61	485 through 616		485 through 616	617		<u> • </u>
62	54 through 995	54 through 227	228 through 995	 		669 through 682
63	657 through 923	657 through 896	897 through 923	996	1130 through 1135	1181 through 1191
64	18 through 311	18 through 62		924	957 through 962	974 through 1008
65	151 through 426	151 through 258	63 through 311	312	•	·
66	10 through 1062	10 through 57	259 through 426	427	505 through 510	527 through 538
67	78 through 491		58 through 1062	1063	1710 through 1715	1735 through 1747
68	69 through 371	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
69	2 through 757	69 through 287	288 through 371	372	510 through 515	530 through 542
70	2 through 1051	2 through 205	206 through 757	758		1160 through 1174
71	2 through 1171	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
72		2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
73	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
74	62 through 916	62 through 757	758 through 916		•	904 through 916
75	62 through 520	·	62 through 520	521	1124 through 1129	1141 through 1153
76	21 through 167		21 through 167	168		
77	22 through 318		94 through 318	319	497 through 502	516 through 526
	8 through 292		119 through 292	293	317 through 322	339 through 352
78	16 through 378	16 through 84	85 through 378	379	502 through 507	522 through 542





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COME TABLE III

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	80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
	81	47 through 541	47 through 220	221 through 541	542		597 through 605
	82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
	83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
	84	89 through 382	•	89 through 382	383		408 through 420
$-\Gamma$	85	80 through 415	80-through 142	143 through 415	416	471 through 476	488 through 501
	86	152 through 361	152 through 283	284 through 361	362		
Γ	87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
Γ	88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
	89	199 through 802		199 through 802	 	780 through 785	791 through 802
Γ	90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
Γ	91	26 through 361	- ·	26 through 361	+		350 through 361
	92	3 through 131		3 through 131	132		591 through 605
	93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
	94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	
	95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1139 through 1150
3	36	327 through 417		327 through 417	1		1504 through 1513
3	17	63 through 398	63 through 206	207 through 398	399	<u> </u>	404 through 417
9	8	2 through 163		2 through 163	164	488 through 493	F11 4b + F00
9	9	13 through 465	13 through 75	76 through 465	466		511 through 522
1	00	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1022 through 1041
1	D1	103 through 294	103 through 243	244 through 294	295		1023 through 1041
1	02	81 through 518	81 through 173	174 through 518	519	- -	1
11	03	66 through 326	·	66 through 326	327	1066 through 1071	
11	04	170 through 289	170 through 250	251 through 289	290		1087 through 1098
10)5	36 through 497	1.	36 through 497	498	650 through 655	663 through 685
10	6	18 through 320		18 through 320	321	539 through 544	542 through 554
10	17	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
10	8	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
10	9	84 through 332	84 through 170	171 through 332	333	·	702 through 714
11	0	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
11	1	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
11	2	26 through 562	26 through 187	188 through 562	563		775 tti dugit 767
11.	3	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	1	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	5	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	3	25 through 399	25 through 186	187 through 399	400		
117	'	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118		72 through 704	72 through 161	162 through 704	705	772 through 777	. 102 11100001 11/3
119	4	14 through 505	44 through 223	224 through 505	506	·	·
120	7	25 through 393	SE :	151 through 393	394	734 through 739	757 through 770
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CONT. TABLE IV

CONT. TABLE IV						
121	58 through 1095	58 through 114	115 through 1095	1096		1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659		440 through 659	•	601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	1.
128	121 through 477	121 through 288	289 through 477			 •
129	2 through 163		2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62.through 385	•	62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231	·	124 through 231	232		387 through 400
134	131 through 1053	131 through 169	170 through 1053	1.	1019 through 1024	
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382		875 through 886
138	46 through 579	46 through 156	157 through 579	580	 	
139	92 through 471	92 through 172	173 through 471	 . 	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559		1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674		1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
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CONT. TABLE IV

C	ONT. TABLE IV					
2	64 42 through 299	42 through 101	102 through 299	300		762 shrough 775
2	65 198 through 43	1 198 through 26	0 261 through 431		- .	762 through 775
20	66 279 through 47	3 279 through 36	2 363 through 473		944 through 949	970 through 981
26	67 12 through 644	12 through 92	93 through 644	645	1002 through 100	
28	38 91 through 459	91 through 330	331 through 459			
26	9 70 through 327	70 through 147			1741 through 1746	1271 through 1281
27	0 12 through 497	12-through-104			935 through 940	The through 1774
27	1 90 through 383	90 through 200	201 through 383	384	609 through 614	955 through 967
27	2 332 through 541	332 through 376		542	739 through 744	632 through 643
27	3 43 through 222	43 through 177	178 through 222	223	530 through 535	761 through 773
27	4 115 through 231	115 through 180		232	419 through 424	555 through 566
27	5 232 through 384	232 through 300		385	650 through 655	445 through 455
276	143 through 427	143 through 286		428		662 through 673
277	284 through 463	294 through 379		464	606 through 611	628 through 639
278	3 162 through 671	162 through 398		672	905 shared 046	762 through 772
279	63 through 632	63 through 308	309 through 632	633	805 through 810	830 through 840
280	21 through 362	21 through 200	201 through 362	363	808 through 813	829 through 840
281	21 through 503	21 through 344	345 through 503	504	821 through 826	838 through 849
282	1 through 201	1 through 63	64 through 201		1305 through 1310	1330 through 1341
283		39 through 134		202	637 through 642	660 through 671
284	69 through 263	69 through 125	135 through 1034	1035	1566 through 1571	1587 through 1597
285	115 through 285	115 through 204		264	1173 through 1178	1196 through 1205
286	90 through 344	90 through 140	205 through 285	286	505 through 510	525 through 536
287	57 through 311	57 through 107	141 through 344	345	500 through 505	515 through 527
288	96 through 302	96 through 182	108 through 311	312	467 through 472	482 through 493
289	161 through 526	161 through 328	183 through 302	303	·	501 through 514
290	210 through 332	210 through 299	329 through 526	527	•	799 through 811
291	212 through 361		300 through 332	333	594 through 599	613 through 625
292	75 through 482	212 through 319	320 through 361	362	650 through 655	673 through 684
293	50 through 631	75 through 128	129 through 482	483	595 through 600	618 through 627
294	154 through 576	50 through 244	245 through 631	632	777 through 782	801 through 812
295	154 through 897	154 through 360	361 through 576	577	737 through 742	763 through 775
296	146 through 292	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
297	126 through 383	146 through 253	254 through 292	293	395 through 400	433 through 444
298	66 through 497	126 through 167	168 through 383	384	726 through 731	743 through 754
299	49 through 411	66 through 239	240 through 497	498	594 through 599	618 through 629
300-	49 through 534	49 through 96	97 through 411	412	732 through 737	750 through 763
301		49 through 96	97 through 534	535	593 through 598	612 through 623
302	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
303	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
	32 through 328	32 through 103	104 through 328	329	508 through 513	528 through 539
304	21 through 527	21 through 95	96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647			





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CONT. TABLE IV

	DIVI. TABLE IV					•
30			307 through 471	472	663 through 668	682 through 693
30		74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
30		48 through 89	90 through 164	165	482 through 487	505 through 517
30			296 through 334	335	355 through 360	392 through 405
311		195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
31		90 through 179	180 through 815	816	883 through 888	905 through 916
312		52 through 231	232 through 513	514	553 through 558	572 through 583
313		172 through 354	355 through 438	439	682 through 687	685 through 697
314		148 through 225	226 through 366	367	770 through 775	792 through 803
315		175 through 276	277 through 336	337	. 1	812 through 823
316		191 through 304	305 through 553	554	766 through 771	804 through 817
317		106 through 216	217 through 603	604		1102 through 1112
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
320	44 through 814	44 through 112	113 through 814	815	1.	978 through 989
321	3 through 581	3 through 182	183 through 581	582	 	1006 through 1016
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
324	201 through 332	201 through 251	252 through 332	333		869 through 880
325	217 through 543	217 through 255	256 through 543	544	 .	1206 through 1217
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
331	672 through 752	672 through 722	723 through 752	753		1150 through 1161
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
333	80 through 232	80 through 127	128 through 232	233	617 through 622	
334	91 through 291	91 through 219	220 through 291	292	367 through 372	634 through 645 389 through 400
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
336	54 through 590	54 through 227	228 through 590	591		955 through 965
337	133 through 846	133 through 345	346 through 846	847		890 through 901
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	
339	124 through 411	124 through 186	187 through 411	412	948 through 953	1338 through 1347
340	372 through 494	372 through 443	444 through 494	495	708 through 713	971 through 983
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	732 through 745
342	117 through 866	117 through 170	171 through 866	867	<u> </u>	1095 through 1106
343	13 through 465	13 through 75	76 through 465	466	1159 through 1164	1178 through 1190
344	2 through 718	2 through 76	77 through 718	719	1035 through 1040	1060 through 1070
345	86 through 709		362 through 709		1170 through 1175	1203 through 1213
346	63 through 320		180 through 320	710	943 through 948	963 through 973
347	299 through 418			321	771 through 776	799 through 810
			Joo undugn 418	419	739 through 744	762 through 771





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CONT. TABLE IV

	SILLY LUDEL IA					•
34	8 186 through 380	186 through 233	234 through 380	381	383 through 388	206 45 400
34	9 69 through 458	69 through 233	234 through 458	}	564 through 569	396 through 409
35	0 12 through 638	12 through 263	264 through 638		951 through 956	602 through 613
35	1 282 through 389	282 through 332				975 through 985
352	2 208 through 339			340	1413 through 1418	
353	69 through 557	69 through 224	225 through 557	558		1631 through 164
354	134 through 325	134 through 274	275-through-325		849 through 854	870 through 883
355		78 through 227	228 through 731	326		718 through 729
356		46 through 90		732		1002 through 1013
357		126 through 182	91 through 693	694	937 through 942	962 through 973
358			183 through 527	528	834 through 839	856 through 867
359	73 through 948	66 through 113	114 through 320	321	490 through 495	508 through 519
360	69 through 434	73 through 159	160 through 948	949		1016 through 1028
361		69 through 236	237 through 434	435	419 through 424	441 through 452
362	628 through 804	628 through 711	712 through 804	805		864 through 875
	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435		618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613		839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186		906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	458 through 471
372	274 through 597	274 through 399	400 through 597	598	731 through 736	1493 through 1504
373	230 through 469	230 through 307	308 through 469	470		754 through 765
74	72 through 545		204 through 545	546	1004 through 1009	1027 through 1040
75	36 through 425		120 through 425		1215	1151 through 1162
76	155 through 751		341 through 751	426	1215 through 1220	1240 through 1250
77	46 through 585			752	912 through 917	937 through 947
		anough 120	121 through 585	586	584 through 589	606 through 619



			
ld	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55		1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180		1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	
151	1 through 7	•	1 through 97
152	-42 through 157	-42 through ·1	1 through 7
153	1 through 43		1 through 157
154	-37 through 13	-37 through -1	1 through 43
155	1 through 153	·	1 through 13
156	1 through 67		1 through 153
157	1 through 87		1 through 67
158	-85 through 165	-85 through -1	1 through 87
159	1 through 24	·	1 through 165
160	1 through 228		1 through 24
161	-20 through 66	-20 through -1	1 through 228
162	1 through 44	- Lindagii 1	1 through 66
163	-58 through 256	-58 through -1	1 through 44
164	-80 through 9	-80 through -1	1 through 256
165	-15 through 83	-15 through -1	1 through 9
166	-36 through 56	-36 through -1	1 through 83
167	-16 through 335	-16 through -1	1 through 56
168	-47 through 91	-47 through -1	1 through 335
169	-73 through 28	-73 through -1	1 through 91
170	-68 through 184	-68 through -1	1 through 28
171	-68 through 282	-68 through -1	1 through 184
172	-68 through 322	-68 through -1	1 through 282
173	-82 through 108	-82 through -1	1 through 322
174	-232 through 53	-232 through -1	1 through 108
175	1 through 153	Zoz mogn-y	1 through 53
176	1 through 49		1 through 153
177	-24 through 75	-24 through -1	1 through 49
178	-37 through 58	-37 through -1	1 through 75
179	-23 through 98	-23 through -1	1 through 58
180	1 through 59	25 through -	1 through 98
181	·14 through 72	-14 through -1	1 through 59
182	-58 through 107	-58 through -1	1 through 72
183	-35 through 45	-35 through -1	1 through 107
184	-21 through 52	-21 through -1	1 through 45
185	1 through 98	z i mondii i	1 through 52
186	-21 through 91	-21 through -1	1 through 98
187	-44 through 26	-44 through -1	1 through 91
188	-13 through 79	-13 through -1	1 through 26
189	-42 through 165	-42 through -1	1 through 79
190	1 through 201	-72 miougn -1	1 through 165
	<u> </u>		1 through 201







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CONT. TABLE V

	CONT. TAI	BLE V		
	191	-37 through 342	-37 through -1	1 41
	192	1 through 112	·	1 through 342
	193	1 through 43		1 through 112
	194	-16 through 35	-16 through -1	1 through 43
	195	-18 through 226	-18 through -1	1 through 35
	196	-34 through 319	-34 through -1	1 through 226
	197	1 through 30	- Cranough -	1 through 319
	198	-48 through 64	-48 through -1	1 through 30
_	199_	1 through 54	· · · · · ·	1 through 64
	200	-21 through 130	-21 through -1	1 through 54
	201	-25 through 203	-25 through -1	1 through 130
	202	-47 through 17	-47 through -1	1 through 203
	203	-31 through 115	-31 through -1	1 through 17
	204	1 through 87	·	1 through 115
	205	-27 through 13	-27 through -1	1 through 87
	206	1 through 154	·	1 through 13
	207	1 through 101		1 through 154
	208	-22 through 434	-22 through -1	1 through 101
	209	-17 through 81	-17 through -1	1 through 434
	210	-29 through 54	-29 through -1	1 through 81
	211	-23 through 206	-23 through -1	1 through 54
	212	-21 through 131	-21 through -1	1 through 206
	213	-54 through 125	-54 through -1	1 through 131
I	214	-92 through 177	-92 through -1	1 through 125
	215	-22 through 113	-22 through -1	1 through 177
	216	-38 through 29	-38 through -1	1 through 113
ŀ	217	-54 through 71	-54 through -1	1 through 29
ŀ	218	-21 through 355	-21 through -1	1 through 71
	219	-30 through 181	-30 through -1	1 through 355
L	220	-60 through 94	-60 through -1	1 through 181
Ļ	221	-42 through 81	-42 through -1	1 through 94
-	222	-19 through 327	-19 through -1	1 through 81 1 through 327
_	223	-20 through 190	-20 through -1	1 through 190
-	224	-20 through 164	-20 through -1	1 through 164
-	225	-22 through 205	-22 through -1	1 through 705
-	226	-41 through 33	-41 through -1	1 through 33
	227	1 through 73		1 through 73
-	228	-16 through 66	-16 through -1	1 through 75
-	229	-56 through 63	-56 through -1	1 through 63
	230	1 through 54		1 through 54
-	231	-14 through 196	-14 through -1	1 through 196
_	232	1 through 108	•	1 through 108
	233	-18 through 25	-18 through -1	1 through 25
-	234	1 through 36		1 through 36
-	235	-13 through 294	-13 through -1	1 through 294
-	236	-32 through 74	-32 through -1	1 through 74
_		-19 through 23	-19 through -1	1 through 23
	238	-20 through 97	-20 through -1	1 through 97
_	240	-37 through 141	-37 through -1	1 through 141
	241	-27 through 99	-27 through -1	1 through 99
	378	-115 through 59	-115 through -1	1 through 59
_	378	-20 through 32	-20 through -1	1 through 32
-	380	-23 through 170	-23 through -1	1 through 170
	000	-14 through 68	-14 through -1	1 through 68
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CONT. TABLE V

CUNT. TABLE V			
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through ·1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	
395	-24 through 49	-24 through -1	1 through 37
396	-18 through 42	-18 through -1	1 through 49
397	-93 through 99	-93 through -1	1 through 42
398	-72 through 77	-72 through -1	1 through 99
399	-20 through 53	-20 through -1	1 through 77
400	-20 through 66	-20 through -1	1 through 53
401	-21 through 57		1 through 66
402	-28 through 37	-21 through -1	1 through 57
403	-27 through 184	-28 through -1	1 through 37
404	-80 through 43	-27 through -1	1 through 184
405	-26 through 60	-80 through -1	1 through 43
406	-31 through 131	-26 through -1	1 through 60
407	-37 through 61	-31 through -1	1 through 131
408	-15 through 55	-37 through -1	1 through 61
409	-45 through 15	-15 through -1	1 through 55
410	-22 through 17	-45 through -1	1 through 15
411		-22 through -1	1 through 17
412	-23 through 28	-23 through -1	1 through 28
413	-48 through 47	-48 through -1	1 through 47
414	-32 through 28	-32 through -1	1 through 28
415	·79 through 91	-79 through -1	1 through 91
416	-82 through 108	-82 through -1	1 through 108
417	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
419	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	1 through 46
422	-30 through 27	-30 through -1	1 through 27
	-17 through 68	-17 through -1	1 through 68
424	-17 through 68	-17 through -1	1 through 68
425	-29 through 40	-29 through -1	1 through 40
426	-56 through 66	-56 through -1	1 through 66
427	-30 through 11	-30 through -1	1 through 11
428	-36 through 14	-36 through -1	1 through 14
429	-18 through 118	-18 through -1	1 through 118
430	-65 through 129	-65 through -1	1 through 129
431	-69 through 72	-69 through -1	1 through 72
			[
432	-69 through 179	-69 through -1	
432 433	-69 through 179 -36 through 13		1 through 179
432	-69 through 179	-69 through -1	





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CONT. TABLE V

CUNT. TABL	<u>E V</u>		•
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	
440	-24 through 75	-24 through -1	1 through 56
441	-25 through 144	-25 through -1	1 through 75
442	-76 through 91	-76 through -1	1 through 144
··· 443	-15 through 55	-15 through -1	1 through 91
444	-33 through 348	-33 through -1	1-through 55
445	-14 through 25	-14 through -1	1 through 348
446	-37 through 13	-37 through -1	1 through 25
447	-26 through 25	-26 through -1	1 through 13
448	-30 through 212	-30 through -1	1 through 25
449	-60 through 94	-60 through -1	1 through 212
450	-61 through 28	-61 through -1	1 through 94
451	-26 through 47	-26 through -1	1 through 28
452	-34 through 20	-34 through -1	1 through 47
453	-38 through 83	-38 through -1	1 through 20
454	-37 through 129	-37 through -1	1 through 83
455	-26 through 154		1 through 129
456	-64 through 27	-26 through -1 -64 through -1	1 through 154
457	-23 through 234	-23 through -1	1 through 27
458	-60 through 133		1 through 234
459	·28 through 79	-60 through -1	1 through 133
460	-13 through 108	-28 through -1	1 through 79
461	-17 through 27	-13 through -1	1 through 108
462	·13 through 96	-17 through -1	1 through 27
463	-41 through 102	-13 through -1	1 through 96
464	-30 through 202	-41 through -1	1 through 102
465	-21 through 40	-30 through -1	1 through 202
466	-19 through 15	-21 through -1	1 through 40
467	-54 through 161	·19 through ·1	1 through 15
468	-17 through 10	-54 through -1	1 through 161
469	-24 through 61	-17 through -1	1 through 10
470	-16 through 35	-24 through -1	1 through 61
471	-43 through 24	-16 through -1	1 through 35
472	-15 through 48	-43 through -1	1 through 24
473	-58 through 121	-15 through -1	1 through 48
474	-71 through 167	-58 through -1	1 through 121
475	-37 through 141	-71 through -1	1 through 167
476	-21 through 75	-37 through -1	1 through 141
477	-24 through 17	-21 through -1	1 through 75
478	-27 through 86	-24 through -1	1 through 17
479	-18 through 232	-27 through -1	1 through 86
480	-21 through 130	-18 through -1	1 through 232
481	-21 through 130	-21 through -1	1 through 130
482	-92 through 116	·25 through ·1	1 through 214
483	-39 through 47	·92 through ·1	1 through 116
484	-27 through 13	-39 through -1	1 through 47
485	-16 through 49	-27 through -1	1 through 13
486	-55 through 75	·16 through ·1	1 through 49
487	-84 through 125	-55 through -1	1 through 75
488	-17 through 19	-84 through -1	1 through 125
489	-29 through 15	-17 through -1	1 through 19
- 	-29 (11100)(11 15	-29 through -1	. 1 through 15



490	-52 through 111	-52 through -1	1 through 111
491	-47 through 17	-47 through -1	1 through 111
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201	-15 through -1	1 through 168
494	-19 through 115		1 through 201
495	-16 through 69	-19 through -1	1 through 115
496	-29 through 263	-16 through -1	1 through 69
497	-56 through 66	-29 through -1	1 through 263
498		-56 through -1	1 through 66
499	-28 through 31	-28 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
501	-13 through 86	-13 through -1	1 through 86
	-25 through 83	-25 through -1	1 through 83
502	-15 through 168	-15 through -1	1 through 168
503	-15 through 83	-15 through -1	1 through 83
504	-57 through 126	-57 through -1	1 through 126
505	-14 through 126	-14 through -1	
506	-14 through 45	-14 through -1	1 through 126
507	-36 through 65	-36 through -1	1 through 45
508	-55 through 286	-55 through -1	1 through 65
509	-42 through 66	-42 through -1	1 through 286
510	-26 through 54	-26 through -1	1 through 66
511	-44 through 114		1 through 54
512	-28 through 102	-44 through -1	1 through 114
513	-62 through 137	-28 through -1	1 through 102
514	-25 through 155	-62 through -1	1 through 137
	Lo tillugii 100	-25 through -1	1 through 155





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		(ADLE VI
ld	Collection re	fs Deposit Name
40	ATCC # 989	21 SignalTag 121-144
41	ATCC # 989	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 989	21 SignalTag 121-144
43	ATCC # 9892	20 SignalTag 67-90
44	ATCC # 9892	
45	ATCC # 9892	O SignalTag 67-90
46	ATCC # 9892	3 SignalTag 44-66
47	ATCC # 9892	O SignalTag 67-90
48	ATCC # 9892	
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	
52	ATCC # 98920	•
3	ATCC # 98923	
4	ATCC # 98920	
5	ATCC # 98920	SignalTag 67-90
6	ATCC # 98920	SignalTag 67-90
7	ATCC # 98921	SignalTag 121-144
3	ATCC # 98920	SignalTag 67-90
3	ATCC # 98920	SignalTag 67-90
1	ATCC # 98920	Signal Tag 67-90
_	ATCC # 98923	
	ATCC # 98923	SignalTag 44-66
	ATCC # 98923	SignalTag 44-66
	ATCC # 98922	SignalTag 44-66
	ATCC # 98923	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
	ATCC # 98923	SignalTag 44-66
	ATCC # 98921	SignalTag 121-144
		SignalTag 67-90
	ATCC # 98920	SignalTag 67-90
	ATCC # 98921	SignalTag 121-144
	ATCC # 98921	SignalTag 121-144
	ATCC # 98921	SignalTag 121-144
	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
	ATCC # 98923	SignalTag 44-66



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74	ATCC # 98923	SignalTag 44-66	
75	ATCC # 98920	SignalTag 67-90	
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
78	ATCC # 98921	SignalTag 121-144	
79	ATCC # 98923	SignalTag 44-66	
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
81	ATCC # 98921	SignalTag 121-144	
82	ATCC # 98920	SignalTag 67-90	-
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
84	ATCC # 98923	SignalTag 44-66	
85	ATCC # 98923	SignalTag 44-66	
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
87	ATCC # 98923	SignalTag 44-66	
88	ATCC # 98923	SignalTag 44-66	
89	ATCC # 98923	SignalTag 44-66	
90	ATCC # 98923	SignalTag 44-66	
91	ATCC # 98923	SignalTag 44-66	
92	ATCC # 98920	SignalTag 67-90	
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
94	ATCC # 98923	SignalTag 44-66	\dashv
95	ATCC # 98923	SignalTag 44-66	\dashv
96	ATCC # 98920	SignalTag 67-90	\neg
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
98	ATCC # 98921	SignalTag 121-144	
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
100	ATCC # 98921	SignalTag 121-144	\neg
101	ATCC # 98920	SignalTag 67-90	_
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\neg
05	ATCC # 98921	SignalTag 121-144	
06	ATCC # 98920	SignalTag 67-90	\dashv
07	ATCC # 98920	SignalTag 67-90	\dashv
08	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\neg
09	ATCC # 98923	SignalTag 44-66	\dashv
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\dashv





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111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120.
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
40	ECACC # 98121506	SignalTag 11121998
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TABLE VII

Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CL0_2	44	DNA
26-27-3-D7-CL0_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
` 26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CL0_1	48	DNA
27-1-2-B3-CL0_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	65	DNA
47-14-1-C3-CLO_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48·1·1·H7·CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA





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		,
48-54-1-G9-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CL0_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	- 87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA





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	•	1	4	i.

30-12-3-G5-CL0_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CL0_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CL0_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT





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		-126-
26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CLO_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51:15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CLO_2	183	PRT
51-34-3-F8-CLO_2	184	PRT



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	<u> </u>	127-
57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CL0_3	211	PRT
30-12-3-G5-CL0_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CLO_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

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57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CL0_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
20-6-1-D11-FL2	242	DNA
20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA





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33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-87-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-B8-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
51-1-1-G12-FL1	293	DNA
51-1-4-E9-FL3	294	DNA

295

DNA

51-1-4-E9-FL2





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	51-2-1-E10-FL1		296		DNA	
	51-2-3-F10-FL1		297		DNA	
	51-2-4-F5-FL1		298		DNA	_
	51-3-3-B10-FL2		299		DNA	
	51-3-3-B10-FL3		300		DNA	
	51-7-3-G3-FL1		301		DNA	
	51-10-3-D11-FL1		302		DNA	
	51-11-3-D5-FL1		303		DNA	
	51-13-1-F7-FL3		304		DNA	
	51-15-4-H10-FL1		305	\neg	DNA	
	51-17-4-A4-FL1		306	\neg	DNA	
	51-18-1-C3-FL1		307	\top	DNA	
	51-25-3-F3-FL1		308		DNA	
-	51-27-1-E8-FL1		309	_	DNA	
	51-28-2-G1-FL2		310		DNA	
	51-39-3-H2-FL1		311	1	DNA	_
	51-42-3-F9-FL1		312	1	DNA	_
L	51-44-4-H4-FL1		313	+	DNA	\dashv
L	55-1-3-H10-FL1		314	1	DNA	\dashv
L	55-5-4-A6-FL1		315	1	DNA	\dashv
L	58-26-3-D1-FL1		316	 	DNA	\dashv
L	57-18-1-D5-FL1		317	_	DNA	\dashv
L	57-27-3-A11-FL1		318	+	DNA	\dashv
	57-27-3-G10-FL2		319	+	DNA	\dashv
	58-10-3-D12-FL1		320	 	DNA	\dashv
	58-11-1-G10-FL1		321	 	DNA	\dashv
	58-11-2-G8-FL2		322		DNA	\dashv
	58-36-3-A9-FL2		323		DNA	\dashv
_	58-38-1-A2-FL2		324		DNA	\dashv
	58-38-1-E5-FL1		325		DNA	\dashv
	58-44-2-B3-FL3		326		DNA	-
	58-45-3-H11-FL1	7-	327		DNA	╬
	58-53-2-B12-FL2		328		DNA	1
	59-9-4-A10-FL1		329		DNA	+
	60-16-3- A6-F L1		330		DNA	1
	60-17-3-G8-FL2		331		DNA	1
_	62-5-4-B10-FL1		332		DNA	1
						1





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		-131-		
65-4-4-H3-FL1	333	DNA		
74-3-1-89-FL1	334	DNA		
76-4-1-G5-FL1	335	DNA		
76-7-3-A12-FL1	336	DNA		
76-16-4-C9-FL3	337	DNA		
76-30-3-B7-FL1	338	DNA		
77-5-1-C2-FL1	339	DNA		
77-5-4-E7-FL1	340	DNA		
77-11-1-A3-FL1	341	DNA		
77-16-3-D7-FL1	342	DNA		
77-16-4-G3-FL1	343	DNA		
77-25-1-A6-FL1	344	DNA		
77-26-2-FL3	345	DNA		
78-6-2-E3-FL2	346	DNA		
78-7-1-G5-FL2	347	DNA		
78-16-2-C2-FL1	348	DNA		
78-18-3-B4-FL3	349	DNA		
78-20-1-G11-FL1	350	DNA		
78-22-3-E10-FL1	351	DNA		
78-24-2-B8-FL1	352	DNA		
78-24-3-A8-FL1	353	DNA		
78-24-3-H4-FL2	354	DNA		
78-25-1-F11-FL1	355	DNA		
78-26-1-B5-FL1	356	DNA		
78-27-3-D1-FL1	357	DNA		
78-29-1-B2-FL1	358	DNA		
78-29-4-B6-FL1	359	DNA		
14-1-3-E6-FL1	360	DNA		
30-9-1 -G 8-FL2	361	DNA		
33-10-4-H2-FL2	362	DNA		
33-10-4-H2-FL1	363	DNA		
74-10-3-C9-FL2	364	DNA		
33-97-4-G8-FL3	365	DNA		
33-97-4-G8-FL2	366	DNA		
33-104-4-H4-FL1	367	DNA		
47-2-3-B3-FL1	368	DNA		
47-37-4-G11-FL1	369	DNA		
	<u> </u>			





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57-25-1-F10-FL2	370	DNA	
58-19-3-D3-FL1	371	DNA	
58-34-3-C9-FL2	372	DNA	
58-48-4-E2-FL2	373	DNA	
76-21-1-C4-FL1	374	DNA	
78-26-2-H7-FL1	375	DNA	
77-20-2-E11-FL1	376	DNA	
47-1-3-F7-FL2	377	DNA	
20-6-1-D11-FL2	378	PRT	
20-8-4-A11-FL2	379	PRT	
22-6-2-C1-FL2	380	PRT	
22-11-2-H9-FL1	381	PRT	
23-8-3-B1-FL1	382	PRT	
24-3-3-C6-FL1	383	PRT	
24-4-1-H3-FL1	384	PRT	
26-45-2-C4-FL2	385	PRT	
26-48-1-H10-FL1	386	PRT	
26-49-1-A5-FL2	387	PRT	
30-6-4-E3-FL3	388	PRT	
33-6-1-G11-FL1	389	PRT	
33-8-1-A3-FL2	390	PRT	
33-11-3-C6-FL1	391	PRT	
33-14-4-E1-FL1	392	PRT	
33-21-2-D5-FL1	393	PRT	
33-26-4-E10-FL1	394	PRT	
33-27-1-E11-FL1	395	PRT	
33-28-4-D1-FL1	396	PRT	
33-28-4-E2-FL2	397	PRT	
33-30-4-C4-FL1	398	PRT	
33-35-4-F4-FL1	399	PRT	
33-36-3-F2-FL2	400	PRT	
33-52-4-F9-FL2	401	PRT	
33-52-4-H3-FL1	402	PRT	
33-59-1-B7-FL1	403	PRT	
33-71-1-A8-FL1	404	PRT	
33-72-2-B2-FL1	405	PRT	
33-105-2-C3-FL1	406	PRT	





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		133.
33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	





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		-104.
51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9-4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT





77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT-
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT
		• • • • • • • • • • • • • • • • • • • •







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TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature





WHAT IS CLAIMED IS:

A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242 377 or a sequence complementary thereto.

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- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
 - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.
 - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- 7. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
 - A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
 - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:





obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

cDNA.

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- The method of Claim 13, further comprising the step of isolating said protein. 14.
- 15. A protein obtainable by the method of Claim 14.
- 16. A host cell containing a recombinant nucleic acid of Claim 1.
- A purified or isolated antibody capable of specifically binding to a protein having the sequence of one 17. of SEQ ID NOs: 141-241 and 378-513.
- In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising 10 18. inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent 19. 15 conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
 - A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive 20. amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

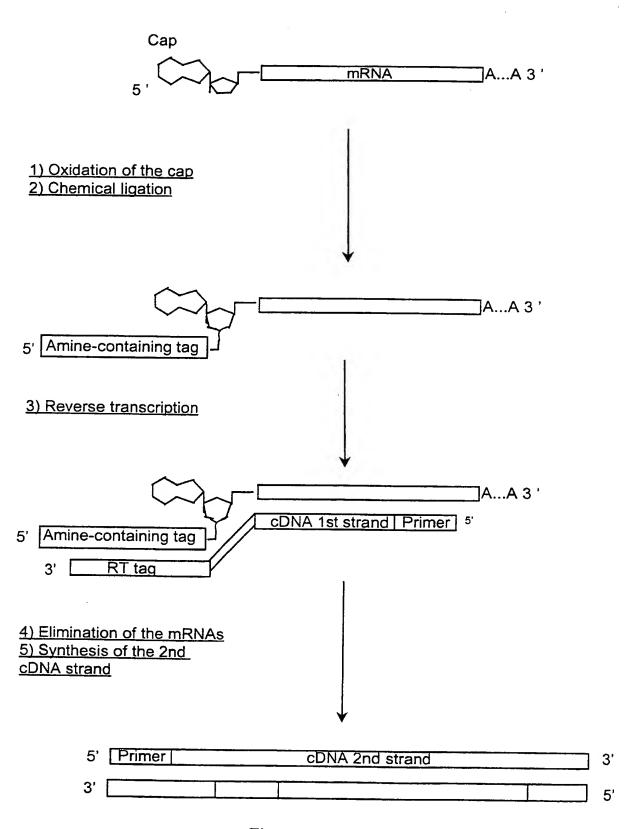


Figure 1



Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

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influence of minimum score on signal peptide recognition

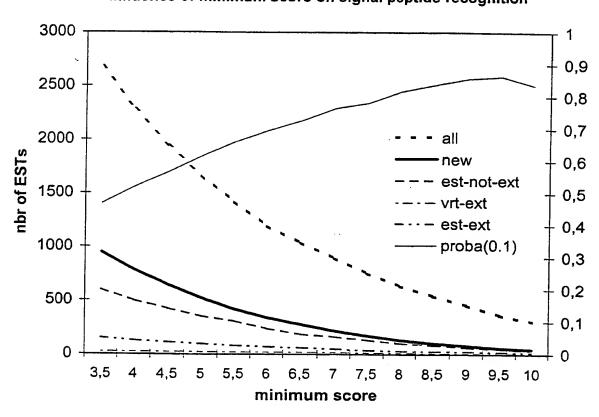


FIGURE 3

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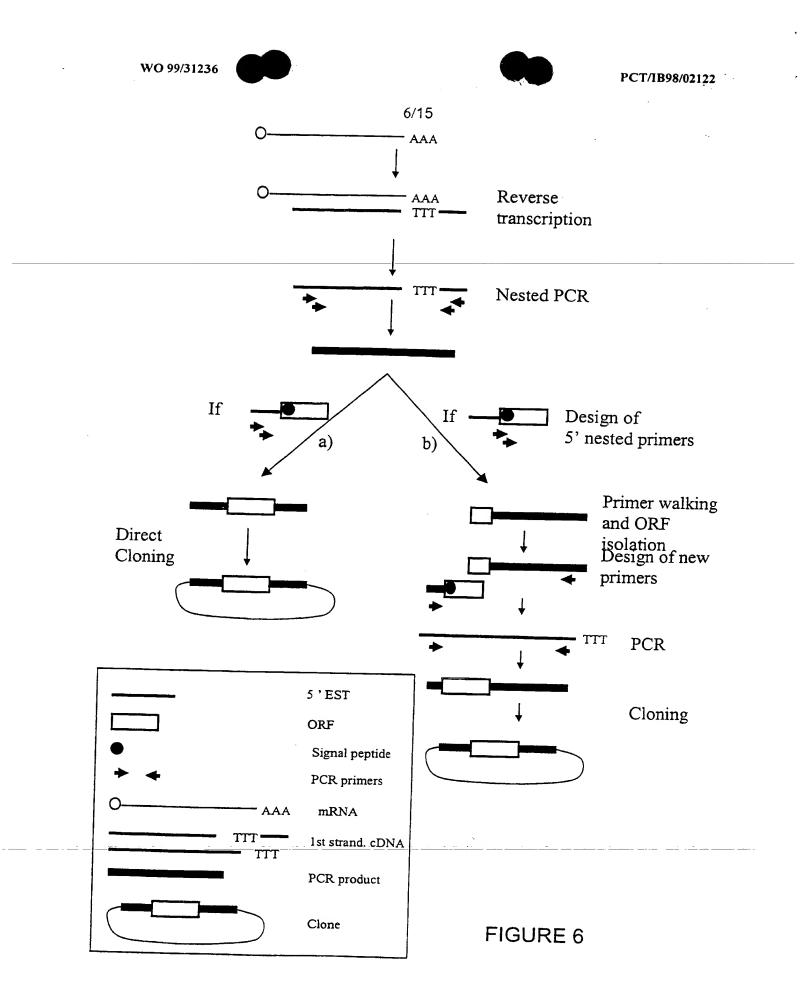


		T	T		
Minimum signal peptide score	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

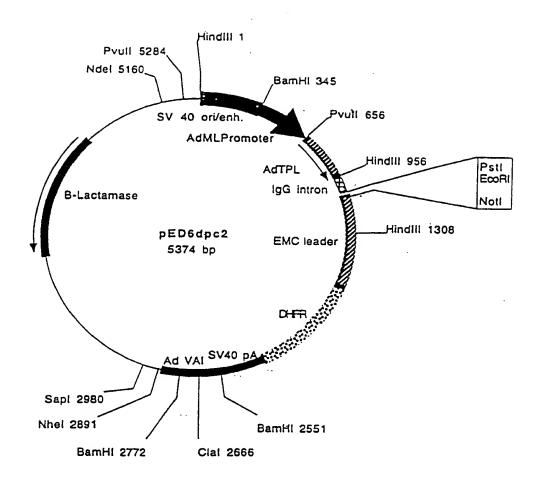
FIGURE 4

Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	Ö	6
Colon	21	11	4	0	o
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	, <u>, </u>
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	Ó	0
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	ő
Large intestine	21	8	4	0	4
Liver	23	9	6	0	ò
Lung	24	12	4	Ö	1
Lung (celis)	57	38	6	ő	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	Ö	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	Ö	1
Placenta	24	5	1	0	ò
Prostate	34	16	4	ő	2
Spleen	56	28	10	Õ	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3		ŏ
Testis	131	68	25	1	8
Thyroid	17	8	2	ó	
Umbilical cord	55	17	12	1	2 3
Uterus	28	15	3	Ö	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150

FIGURE 5



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Plasmid name: pED6dpc2 Plasmid size: 5374 bp



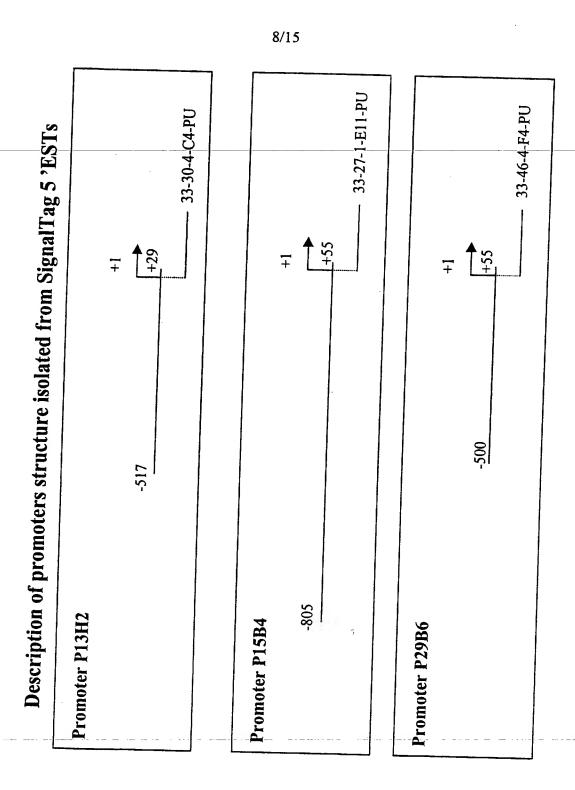


FIGURE 8



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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	- .	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	11	GCACACCTCAG
GATA_C	-364	•	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	•	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	•	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	_	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA
_				U	ACAGGGGA

Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	•	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	•	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
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Figure 9





PCT/IB98/02122

10/15

100.0% identity in 125 aa overlap

SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD

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70 80 90 100 110 120

SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

FIGURE 10





11/15

CLUSTAL W(1.5) multiple sequence alignment

SEQ SEQ	ID ID	NO:	517 232 174 175	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKRIFKIDWTLS
SEQ SEQ	ID ID	NO:	517 232 174 175	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
SEQ	ID ID	NO:	517 232 174 175	KGESQVFKKAVVLHVLPEEPKGTQMLTKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
SEQ SEQ SEQ	ID ID	NO:	232 174	IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN VTRRKHHCVREGSG
SEQ SEQ SEQ	ID ID	NO: NO:	232 174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
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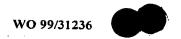
12/15

99.6% identity in 225 aa over?	lap				•
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SEQ ID NO: 231		:::::	::::::::	MLTLLGLSF1	:::::
70 80 SEQ ID NO: 515 VGGACIYKYFMPKST	90 HYRGEMCFFD:	100 SEDPANSLRGG	110		
SEQ ID NO: 231 VGGACIYKYFMPKST	:::::::				
130 140 SEQ ID NO: 515 PVPSFSDSDPAAIIH	150 DFEKGMTAYLI	160 DLLLGNCYLMP	170 LNTSIVMPP	180 KNLVELFGKL	ASGRY
SEQ ID NO: 231 PVPSFSDSDPAAIIH 100					
190 200 SEQ ID NO: 515 LPQTYVVREDLVAVE	210 EIRDVSNLGIF	220 'IYQLCNNRKSI	230 RLRRRDLLI	240 LGFNKRAIDKO	CWKIR
SEQ ID NO: 231 LPQTYVVREDLVAVER		::::::::::::::::::::::::::::::::::::::			
250 260 SEQ ID NO: 515 HFPNEFIVETKICQE ::::::::::::::::::::::::::::::::::::					
220					



13/15

99.7% identity in 353 aa overlap SEQ ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEO ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL





14/15

98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL

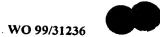
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15/15

68.9% identity in 74 aa overlap

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Duclert, Aymeric
Bougueleret, Lydie

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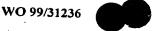
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                                Met Lys Lys Val Leu Leu Leu Ile
                                         -15
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Thr_Ala_Ile_Leu_Ala_Val_Ala_Val_Gly_Phe_Pro_Val_Ser_Gln_Asp_Gln
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caaaattcct gttaataaaa raaaaacaaa tgtaattgaa atagcacaca gcattctcta
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Gln Gly Leu Ser Phe Leu Pro Ser Ala Leu Val Ile Trp Thr Ser	400
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Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu His His Ile	
1 5 10 15	507
gac ccg gct tta cct tat atc agt gac act ggt aca gta gct cca raa Asp Pro Ala Leu Pro Tyr Ile Ser Asp Thr Gly Thr Val Ala Pro Xaa	501
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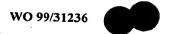


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Ala Xa															
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Ala Pr 30	o Gly	Ser	Thr	Xaa 35	His	Arg	Arg	Lys	Thr	Thr	Arg	Arg	Asn	Tyr 45	
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Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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PCT/IB98/02122

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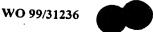
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WO 99/31236
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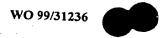
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Phe Leu Ser	aga caa gct atg Arg Gln Ala Met 115	gca gag aac ttt tcc Ala Glu Asn Phe Ser	: atc taataaattt : Ile	481
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Lys	Val	Leu 105	Arg	Asp	Ser	gtg Val	Gln 110	Arg	Leu	Glu	Val	Gln 115	Leu	Arg	Ser		436
AIA	120	Leu	Gly	Pro	Ala	tac Tyr 125	Arg	Glu	Phe	Glu	Val	Leu	Lys	Ala	His	•	484
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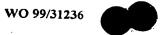
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Leu	Ser	Phe 55	Ile	Ser	Lys	Glu	Glu 60	Met	Lys	Asn	Thr	Ser 65	Trp	Ile	Arg	
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			Leu													
qqa	aca	tac	ttt	tta	caq	agg	tct	qca	aaq	cag		ata	aaa	ttt	caq	386
			Phe													
85		2 -			90	5				95			2		100	
	caa	agc	aaa	caa		agt	att	даа	gag		gtaa	aa t	aaat	attt		436
			Lys							-5					-9	
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			_site													
		- '														
)> 45		acago	rtcat	c ac	raado	ratic		ataca	aca	2220	rcatr	ירם נ	acto	gacag	60
															ccaga	120
															agagat	180
															gaaga	240
			atato													293
	-cac		.cat	,-990	. L at	Lugas	gace	. વલ	1			aa a Sln I		3lu 0		293
cad	+++	200	gag	+~~	+++	tta	222	asa			C 2 2	ato	202			341
			Glu													フェン
at t	c ag	gag	tcc		gaa	agg	ctt	cgt		att	gca	aat	gag		gaa	389



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Ile	Gln	Glu	Ser -45	Ile	Glu	Arg	Leu	Arg	Val	Ile	Ala	Asn	Glu -35	Ile	Glu	
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Leu	-15 agc Ser	cto	agc Ser	att Ile	act Thr	-10 gca Ala	gct Ala	Gly ggg	Val	G1A aaa	-5 ctg Leu	gga Gly	ata Ile	Ala	tct Ser	533
1				5				_	10					15		
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tca Ser	gca Ala	gaa Glu 35	Leu	aca Thr	gcc Ala	agc Ser	agg Arg 40	ctg Leu	act Thr	gca Ala	acc Thr	agc Ser 45	act Thr	gac Asp	caa Gln	629
ttg Leu	gag Glu 50	gca	tta Leu	agg Arg	gac Asp	att Ile 55	ctg	cat His	gac Asp	atc Ile	Thr	ccc	aat Asn	gtg Val	ctt Leu	677
Ser	ttt	gca Ala	ctt Leu	gat Asp	Phe	gac	gaa Glu	gcc Ala	aca Thr	Lys	60 atg Met	att Ile	gcg Ala	aat Asn	Asp	725
			ctc Leu													773
gct Ala	tgg Trp	cga Arg	tat Tyr 100	gta	cct Pro	ata Ile	aat Asn	gtt Val 105	gtt	gag Glu	aca Thr	ctg Leu	aga Arg 110	aca	cgt Arg	821
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Ala	act Thr 130	tca Ser	ggt Gly	gtc Val	ctc Leu	gtt Val 135	gtg Val	ctg Leu	gat Asp	gta Val	gtc Val 140	aac Asn	ctt Leu	gtg Val	caa Gln	917
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Leu	Arg	Gln	tgg Trp	Ala 165	Gln	Glu	Leu	Glu	Glu 170	Asn	Leu	Asn	Glu	Leu 175	acc Thr	1013
His	Ile	His	cag Gln 180	Ser	Leu	Lys	Ala	Gly 185								1060
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ecgg	cego	LC	ccaaa	acco	t gt	CTCC	tgat	aag	atgt	cat	caat	gaca	at c	gtgo	ctgaa	1780
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atta	atec		yryat tosst	2000	. at	tacc	20+-	yaa ~~~	ycag	geg	acct	ccgt	ga c	ccac	accct	1900
atas	acac	to	accca	acct	a ~+	cyyd cetc	40+0	200	aaca	add	acct	getg	gt t	.ttgc	agctt aaaat	1960 2020
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                                                                      120
tgtaaataat tggtagaaaa attctactct gctgtggaat taccaagata atatagacca
                                                                      180
                                                                      240
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tactcctcat ctgtgtaatg aaacagagca tgagtgggaa aaagttaaga gatatttaaa
                                                                      360
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                                                                      420
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                         Met Pro Gly Thr Glu Val Leu Glu Gly Ala
                                                                      520
aca gac gga tta gca gct att aac ctg cta aaa tgg atc aag aca ctt
Thr Asp Gly Leu Ala Ala Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu
                                    -30
                -35
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Gly Gly Ser Val Ile Ser Met Ile Val Leu Leu Ile Cys Val Val Cys
            -20
                                 -15
                                                     -10
ctt tat ata gtc tgt aga tgc gga agc cac ctc tgg aga gaa agc cac
                                                                      616
Leu Tyr Ile Val Cys Arg Cys Gly Ser His Leu Trp Arg Glu Ser His
                                                                      669
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caagcgccca gctatagtta ccaataaagc atggtactgg tattaaaata ggcatgtgtt
                                                                      729
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                                                                     1149
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gtgccaagcc aaaggaacaa ccctggttgt tgaactagca cctaaggtct tagat	
gcgttgctat acagaatctt tggat atg tgc atc agt ggt tta tgc caa	
Met Cys Ile Ser Gly Leu Cys Gln	Ile
1 5	
gtt ggc tgc gat cac cag ctg gga agc acc gtc aag gaa gat aac	tgt 280
Val Gly Cys Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn	
	25
ggg gtc tgc aac gga gat ggg tcc acc tgc cgg ctg gtc cga ggg	
Gly Val Cys Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly	Gln
30 35 40	
tat aaa too cag oto too goa acc aaa tog gat gat act gtg gtt	
Tyr Lys Ser Gln Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val	Ala
45 50 55	
att ccc tat gga agt aga cat att cgc ctt gtc tta aaa ggt cct	
Ile Pro Tyr Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro A	Asp
70	450
cac tta tat ctg gaa acc aaa acc ctc cag ggg act aaa ggt gaa a	aac 472
His Leu Tyr Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu A	Asn
	500
agt ctc agc tcc aca gga act ttc ctt gtg gac aat tct agt gtg g Ser Leu Ser Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Val A	
	Asp 105
ttc cag aaa ttt cca gac aaa gag ata ctg aga atg gct gga cca c	
Phe Gln Lys Phe Pro Asp Lys Glu Ile Leu Arg Met Ala Gly Pro I	Ten
110 115 120	pen
aca gca gat ttc att gtc aag att cgt aac tcg ggc tcc gct gac a	agt 616
Thr Ala Asp Phe Ile Val Lys Ile Arg Asn Ser Gly Ser Ala Asp S	
125 130 135	501
aca gtc cag ttc atc ttc tat caa ccc atc atc cac cga tgg agg g	gag 664
Thr Val Gln Phe Ile Phe Tyr Gln Pro Ile Ile His Arg Trp Arg (31v
140 145 150	
acg gat ttc ttt cct tgc tca gca acc tgt gga gga ggt tat cag o	cta 712
Thr Asp Phe Phe Pro Cys Ser Ala Thr Cys Gly Gly Tyr Gln I	Leu
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WO 99/31236		-28-		PCT/IB98	
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							ctg										101
		-15					Leu -10					- 5					
							cct										149
Pro	Gly 1	Ala	Ala	Gly	Phe 5	Thr	Pro	Ser	Leu	Asp 10	Ser	Asp	Phe	Thr	Phe 15		
							gag										197
Thr	Leu	Pro	Ala	_	Gln	Lys	Glu	Cys		Tyr	Gln	Pro	Met		Leu		
				20					25					30			
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Lys	Ala	Ser		Glu	Ile	Glu	Tyr		Val	Leu	Asp	Gly		Gly	Leu		
			35					40					45				
_		_				_	tct		_	~ ~				_			293
Asp	Ile	-	Phe	His	Leu	Ala	Ser	Pro	Glu	GIY	Lys		Leu	Val	Phe		
	•	50					55					60					
							gtt										341
	65	_	-		_	70	Val				75						
							aat										389
	Tyr	Met	Phe	Cys		Asp	Asn	Thr	Phe		Thr	Ile	Ser	Glu			
80					85					90					95		
				_			ccg	_		_		_	_	_			437
Val	Ile	Phe	Phe		Leu	Ile	Pro	Asp		Met	Gly	Glu	Gln		Gln		
				100					105					110			
							tat										485
Glu	Gln	Glu	_	Trp	Lys	Lys	Tyr		Thr	Gly	Thr	Asp		Leu	Asp		
			115					120					125				
_		_		_		_	gtc	-	_	_		taa	taaa	ata			531
Met	Lys		Glu	Asp	Ile	Leu	Val	Ser	Met	Val	Phe						
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aaaattatta acagccaaaa aaaaaaaaaa										561							

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	gccagcccat tagcccagga ggaggacaag aaacacacgg	171
	ccaacccagc caaggetgte etgaattage aaccetgaca	231
	acaccggaag atccacctag tcaagcccaa ccaagactgg	291
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                                                                      103
Trp Lys Asp Lys Val Val Asp Leu Leu Tyr Trp Arg Asp Ile Lys Lys
                    -30
                                         -25
act gga gtg gtg ttt ggt gcc agc cta ttc ctg ctg ctt tca ttg aca
                                                                      151
Thr Gly Val Val Phe Gly Ala Ser Leu Phe Leu Leu Ser Leu Thr
                -15
                                    -10
gta ttc agc att gtg agc gta aca gcc tac att gcc ttg gcc ctg ctc
                                                                      199
Val Phe Ser Ile Val Ser Val Thr Ala Tyr Ile Ala Leu Ala Leu Leu
tot gtg acc atc agc ttt agg ata tac aag ggt gtg atc caa gct atc
                                                                      247
Ser Val Thr Ile Ser Phe Arg Ile Tyr Lys Gly Val Ile Gln Ala Ile
                        20
cag aaa tca gat gaa ggc cac cca ttc agg gca tat ctg gaa tct gaa
                                                                      295
Gln Lys Ser Asp Glu Gly His Pro Phe Arg Ala Tyr Leu Glu Ser Glu
                    35
                                         40
gtt gct ata tct gag gag ttg gtt cag aag tac agt aat tct gct ctt
                                                                      343
Val Ala Ile Ser Glu Glu Leu Val Gln Lys Tyr Ser Asn Ser Ala Leu
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ggt cat gtg aac tgc acg ata aag gaa ctc agg cgc ctc ttc tta gtt
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Gly His Val Asn Cys Thr Ile Lys Glu Leu Arg Arg Leu Phe Leu Val
            65
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gat gat tta gtt gat tct ctg aag ttt gca gtg ttg atg tgg gta ttt
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Asp Asp Leu Val Asp Ser Leu Lys Phe Ala Val Leu Met Trp Val Phe
                            85
acc tat gtt ggt gcc ttg ttt aat ggt ctg aca cta ctg att ttg gct
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Thr Tyr Val Gly Ala Leu Phe Asn Gly Leu Thr Leu Leu Ile Leu Ala
    95
                        100
ctc att tca ctc ttc agt gtt cct gtt att tat gaa cgg cat cag gca
                                                                      535
Leu Ile Ser Leu Phe Ser Val Pro Val Ile Tyr Glu Arg His Gln Ala
                    115
                                         120
cag ata gat cat tat cta gta ctt gca aat aag aat gtt aaa gat gct
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Gln Ile Asp His Tyr Leu Val Leu Ala Asn Lys Asn Val Lys Asp Ala
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                                     135
atg gct aaa atc caa gca aaa atc cct gga ttg aag cgc aaa gct gaa
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		aacgaacctt				751
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tgtgttcatc	atcttaagta	ttgtaagctg	ctatgtatgg	atttaaaccg	taatcatatc	871
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aaa						994

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ctgcgcccgg gggtcaccaa tgaacagctc tggagtgcac agaaaatcaa gcaggctatt
                                                                      240
ctacatccgg acaccaatga gaagatcttc atg cca ttt aga atg tca ggt tat
                                                                      294
                                 Met Pro Phe Arg Met Ser Gly Tyr
att cct ttt ggg acg cca att gta agt gtt acc ttc aaa gga ttt cct
                                                                      342
Ile Pro Phe Gly Thr Pro Ile Val Ser Val Thr Phe Lys Gly Phe Pro
                        15
ttt cta aaa aat tat ttt aaa tgt cta act tta tgt tat tgc tca cgg
                                                                      390
Phe Leu Lys Asn Tyr Phe Lys Cys Leu Thr Leu Cys Tyr Cys Ser Arg
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                                        35
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Val Phe Asp
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-32-		PCT/IB98/0212
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caa gtt tct caa cag gag gaa ctt aaa taactatgcc aagaattctg	480
Sln Val Ser Gln Gln Glu Glu Leu Lys	
145 150	
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tgaaattta attacggttt gattgatatt tottgaaaac cgccaaagca catatcatca	660
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                                                                      102
Leu Ser Pro Ala Lys Leu Met Met Leu Thr Ile Gly Asp Val Ile Lys
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caa ctg att gaa gcc cac gag cag ggg aaa gac atc gat cta aat aag
                                                                      150
Gln Leu Ile Glu Ala His Glu Gln Gly Lys Asp Ile Asp Leu Asn Lys
gtg aga acc aag aca gct gcc aaa tat ggc ctt tct gcc cag ccc cgc
                                                                      198
Val Arg Thr Lys Thr Ala Ala Lys Tyr Gly Leu Ser Ala Gln Pro Arg
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                                    50
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                                                                      251
Leu Val Asp Ile Ile Ala Ala Val Pro Pro Glu
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Arg Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val	
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Phe Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys	
35 40 45	
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Gly Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln	
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Ala Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp	
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aag ctg gct gaa gag cat tca tcg tgaggggtct ttgtcctctg tactgtctct	595
Lys Leu Ala Glu Glu His Ser Ser	
80 85	
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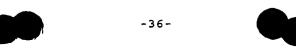
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														Leu		210
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His	Gln	Val	Leu	Glu	Ala	Pro	Gly	Val	Tyr	Val	Phe	Gly	Glu	Leu	Leu	
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Asp	Met	Pro	-35	vaı	Arg	GIU	Leu		Ala	Arg	Asn	Leu	Pro -25	Pro	Leu	
aca	gag	act		aar	aat	220	ctt	-30	cac	ctc	+ ==	att		acc	cta	360
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		-20		- 4 -		2	-15	5				-10				
gct	gct	aaa	gta	aag	tgt	atc	cca	tat	gca	gtg	ttg	ctg	gag	gct	ctt	408
Ala		Lys	Val	Lys	Cys	Ile	Pro	Tyr	Ala	Val	Leu	Leu	Glu	Ala	Leu	
	-5					1				5					10	. = .
														gct		456
Ald	ьеи	Arg	ASII	15	Arg	GIN	Leu	GIU	Asp 20	ьеи	vaı	TTE	GIU	Ala 25	val	
tat	act	gac	ata		cat	aac	tcc	cta		cad	cac	aac	cad	cgg	ctc	504
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-		•	30					35			3		40			
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Ата	11e	Ala	Arg	Inr	Leu	GIN 65	GIU	Trp	Cys	vai	70	Cys	GIU	Val	vai	
cta		aac	att	gag	aaa		ata	900	cat	acc	_	caa	cac	aag	gag	648
Leu	Ser	Glv	Ile	Glu	Glu	Gln	Val	Ser	Ara	Ala	Asn	Gln	His	Lys	Glu	010
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cag	cag	ctg	ggc	ctg	aag	cag	cag	att	gag	agt	gag	gtt	gcc	aac	ctt	696
Gln	Gln	Leu	Gly		Lys	Gln	Gln	Ile		Ser	Glu	Val	Ala	Asn	Leu	
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пуs	пур	TIII	110	пуs	Val	1111	1111	115	Ald	Ата	Ата	Ата	120	Thr	Ser	
caq	qac	cct		caa	cac	cta	act		cta	agg	gaa	cca		cct	aac	792
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	_	125					130					135			-	
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Thr		Gln	Arg	Gln	Pro		Гуs	Lys	Ala	Ser		Gly	Lys	Gly	Leu	
	140					145			.		150					893
	Gly										tgaa	agaa	act s	gregi	ttect	693
155	U		niu	ى برىــ	160	111	001	נעם	501	165						
ccct	9999	gat g	gtggg	gtc		gctgd	ctg	cto	gccto		ggag	gtcct	ca	gagag	geette	953
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cgtt	tctt	aa c	atgt	tgag	ga ga	atgat	tctt	tct	tgg	cct	ggc	catct	cg g	ggaag	gcttga	1553
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Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg
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                                                                      276
                                                                      336
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                                                                      396
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                                                                      456
tctaaaagaa atccaagtac tgtttggtca ttacccctta gtaaaaaaaa gtaacaggag
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agtgggaaag ggaa atg ccg acc aat tgc gct gcg gcg ggc tgt gcc act

•	



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Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp 15 20 25	
cct aaa aga aga aaa gaa tgg gtt cgc ctg gtt agg cgc aaa aat ttt	266
Pro Lys Arg Arg Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe 30 35 40	
gtg cca gga aaa cac act ttt ctt tgt tca aag cac ttt gaa gcc tcc	314
Val Pro Gly Lys His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser	
45 50 55 60	
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Cys Phe Asp Leu Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val	
65 70 75	
cca acc att ttt gat ttt tgt acc cat ata aag tct atg aaa ctc aag	410
Pro Thr Ile Phe Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys	
80 85 90	
tca agg aat ctt ttg aag aaa aac agt tgt tct cca gct gga cca	458
Ser Arg Asn Leu Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro	150
95 100 105	
tot agt tta aaa tca aac att agt agt cag caa gta cta ctt gaa cac	506
Ser Ser Leu Lys Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His	200
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Ser Tyr Ala Phe Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys	554
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ctg gaa aaa gaa ata gca agc tta aga aga aaa atg aaa act tgc cta	602
Leu Glu Lys Glu Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu	
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caa aag gaa cgc aga gca act cga aga tgg atc aaa gcc atg tgt ttg	650
Gln Lys Glu Arg Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu	
160 165 170	
gta aag aat tta gaa gca aat agt gta tta cct aaa ggt aca tca gaa	698
Val Lys Asn Leu Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu	
175 180 185	
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His Met Leu Pro Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys	
190 195 200	
atc ctt gaa caa gat caa caa gat aaa aca ctg cta agt cta aat cta	794
Ile Leu Glu Gln Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu	
205 210 215 220	
aaa cag acc aag agt acc ttc att taaatttagc ttgcacagag cttgatgcct	848
Lys Gln Thr Lys Ser Thr Phe Ile	
225	
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aataaagttt tacttgaagt aacattactg aatttgtgaa gacttgatta caaaagaata	968
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Trp Phe Val His Ser Ser Ala Leu Gly Leu Val Leu Ala Pro Pro Phe	e
-10 -5 1	
tee tet eeg gge act gae eee ace ttt eeg tgt att tae tgt agg et	a 149
Ser Ser Pro Gly Thr Asp Pro Thr Phe Pro Cys Ile Tyr Cys Arg Le	u
5 10 15	
tta aat atg atc atg acc cgc ctt gca ttt tca ttc atc acc tgt tt	a 197
Leu Asn Met Ile Met Thr Arg Leu Ala Phe Ser Phe Ile Thr Cys Le	น
20 25 30 35	
tgc cca aat tta aag gaa gtt tgt ctc att ttg cca gaa aaa aat tg	t 245
Cys Pro Asn Leu Lys Glu Val Cys Leu Ile Leu Pro Glu Lys Asn Cy	s
40 45 50	
aat agt cgg cac gct gga ttt gta ggg cca gca aaa ttg cgg cag	290
Asn Ser Arg His Ala Gly Phe Val Gly Pro Ala Lys Leu Arg Gln	
55 60 65	
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atctatctat ctatctatct atctatctat ctatctat	480
ggct atg tcg ccg agg ctg gag tgc agt ggt gca atc ttg gct cac tgc	529
Met Ser Pro Arg Leu Glu Cys Ser Gly Ala Ile Leu Ala His Cys	
1 5 10 15	
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and dee age ace aca ggs som age and ade ace goo aca got ace age	
Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp	
Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp	626
Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp 20 25 30	626
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Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala Glu
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                            -50
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Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly Val
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                                            -30
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Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His His
                                        -15
                    -20
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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro Cys
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Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala Ile
att gaa gaa gat gat ggt gat ggc gga tgg gta gat aca tat cac aac
                                                                      392
Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His Asn
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aca ggt att aca gga ata acg gaa gcc gtt aaa gag atc aca ctg gaa
                                                                      440
Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu Glu
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aat aag gac aat ata agg ctt caa gat tgc tca gca cta tgt gaa gag
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Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu Glu
                                80
gaa gaa gat gaa gaa gga gaa gct gca gat atg gaa gaa tat gaa 536
Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr Glu
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                                                                      584
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Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
                        110
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			gtt	_		_		gaa	_		-	_	gat	cat His		776
_						_					_			cct Pro		824
_	_		_			_			_			_	_	aaa Lys		872
	_		-	-	-							-		atg Met 230		920
				_			_		-	_				ata Ile	_	968
	gac Asp			_				_	taat	gaag	gag a	agcat	taaaa	at		1015
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4

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															Met	
															-80	•
		agg														707
Arg	Thr	Arg	Thr	Thr -75	Gly	Asn	Pro	Arg	Gly -70	Leu	His	Asp	Thr	Phe	Pro	
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		Pro														
age	tac	tca		cta	ctt	ccc	taa		aaa	ata	200	~==		~~=	ctc	803
		Ser														603
		-45					-40					-35				
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Cys	Gly	Asp	Gln	Leu	Gln	Gly -25	Thr	Glu	Gly	Trp	Leu -20	Glu	Ala	Thr	Gln	
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-15	1	5	1		-10	501	1114	Cyb	71.14	-5	115	Gly	rsp	Gry	1	
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Thr	Gln	Pro	Val 5	Pro	Leu	Cys	Ser									
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					.00 \ -15					-10	ocu (-ys	V G J Z		-5			
~~~	~+~														_			
														gaa			98	
Ala	Val	Leu	Ala	Trp	Gly	Phe	Leu	Trp	Val	$\mathtt{Trp}$	Asp	Ser	Ser	Glu	Arg			
				1				5					10					
atg	aag	agt	cgg	gag	cag	gga	gga	cgg	ctg	gga	gcc	gaa	agc	cgg	acc		146	
														Arg				
	-	15	- 3			2	20	3		1		25		9				
cta	cta		a+ a	~~~		act		~~+	~	~~~							3.04	
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neu		vaı	TTE	Ala	Hls		Asp	Asp	GIU	Ala	Met	Phe	Phe	Ala	Pro			
	30					35					40							
aca	gtg	cta	ggc	ttg	gcc:	cgc	cta	agg	cac	tgg	gtg	tac	ctg	ctt	tgc-		242	
														Leu				
45			•		50	_		_		55		- 2			60			
ttc	tet	gca	att	ttc		agg	gag	cta	aat		t=c	300	~~~	ggt	-		290	
Dhe	Sor	712	Val	Dho	7==	~33	27.5	Tou	290	914	The same	acc	gaa	990	T		290	
	SCI	ALG	vai		Arg	Arg	GIU	neu		GIU	TYL	THE	GIU	Gly	Leu			
				65					70					75				
acc	tct	gaa	CCC	ctc	aca	gcc	tagg	ggaca	agg a	agcgg	geegg	gc tt	acct	ggtg	3		341	
Thr	Ser	Glu	Pro	Leu	Thr	Ala												
			80															
ggti	tagad	aga d	atco	acac	ac to	acat	acta	a car	cago	agg	atte	sagg=	acc s	araca	aaca	~	401	
	دررر	,	J-3	, , , =	,	J-3,		5		~==	~~~	~556	-9C 6	-3436	-uu-u	9	# O T	

ζ





ttgcagttgg ttgtatt tctgtggaac tttttt cgaaacaatc tatgctg	att tgtagaagga	gcaagaatat	tgaccttact		461 521 568
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caagcagctc tgcctttttc tcttgtaagc atg ctt gtc acc cag gga cta gtc  Met Leu Val Thr Gln Gly Leu Val  -35  -30	174
tac caa ggt tat ttg gca gct aat tct aga ttt gga tca ttg ccc aaa  Tyr Gln Gly Tyr Leu Ala Ala Asn Ser Arg Phe Gly Ser Leu Pro Lys  -25 -20 -15	222
gtt gca ctt gct ggt ctc ttg gga ttt ggc ctt gga aag gta tca tac Val Ala Leu Ala Gly Leu Leu Gly Phe Gly Leu Gly Lys Val Ser Tyr -10 -5 1	270
ata gga gta tgc cag agt aaa ttc cat ttt ttt gaa gat cag ctc cgt  Ile Gly Val Cys Gln Ser Lys Phe His Phe Phe Glu Asp Gln Leu Arg  5 10 15 20	318
ggg gct ggt ttt ggt cca cag cat aac agg cac tgc ctc ctt acc tgt Gly Ala Gly Phe Gly Pro Gln His Asn Arg His Cys Leu Leu Thr Cys 25 30 35	366
gag gaa tgc aaa ata aag cat gga tta agt gag aag gga gac tct cag Glu Glu Cys Lys Ile Lys His Gly Leu Ser Glu Lys Gly Asp Ser Gln 40 45 50	414
cct tca gct tcc taaattctgt gtctgtgact ttcgaagttt tttaaacctc Pro Ser Ala Ser 55	466
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aaaaaaaaa aa	538

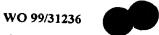
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	gac aag ttc ttc Asp Lys Phe Phe			
	gcc tat gct gag Ala Tyr Ala Glu 70			
,	gac tct ctg gta Asp Ser Leu Val 85	Lys Gln Thr	_	
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	ggc agt ctc tgg Gly Ser Leu Trp			
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Lys Met Asp Cys 160	aag gag tac aac Lys Glu Tyr Asr 165	Tyr Asp Lys	Ser Ile Val 7	Asp Ser
	Leu Arg Leu Pro 180			gca gtc - 627 Ala Val 190
	gca gcc tcc tcc Ala Ala Ser Ser 195		Phe Pro Asp (	Gly Phe 205
	Cag ctg gtg tgc Gln Leu Val Cys			
aac att ttc cca	gtc atc tca cto	tac cta atg	ggt gag gtt a	acc aac 771



Asn	Ile	Phe 225	Pro	Val	Ile	Ser	Leu 230	Tyr	Leu	Met	Gly	Glu 235	Val	Thr	Asn	
cad	tcc		cac	atc	acc	atc	ctt	cca	cag	caa	tac	cta	caa	cca	gtg	819
Cas	Ser	Dhe	Ara	Tle	Thr	Tle	Len	Pro	Gln	Gln	Tvr	Leu	Ara	Pro	Val	
GIII	240	FIIE	Arg	TIC	1111	245		110	01	<b></b>	250		9			
							~~~	~~~	+ ~ +	+			~~~	2+0	+ = =	867
														atc		007
	Asp	vaı	Ala	Thr		GIN	Asp	Asp	Cys		гàг	Pne	Ala	Ile		
255					260					265					270	
														ggc		915
Gln	Ser	Ser	Thr	Gly	Thr	Val	Met	Gly		Val	Ile	Met	Glu	Gly	Phe	
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tac	gtt	gtc	ttt	gat	cgg	gcc	cga	aaa	cga	att	ggc	ttt	gct	gtc	agc	963
Tyr	Val	Val	Phe	Asp	Arg	Ala	Arg	Lys	Arg	Ile	Gly	Phe	Ala	Val	Ser	
_			290	_	-			295					300			
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+++	tat		ctt	aaa	cat	gga		cta	taa	cta	caa	cat	tcc	aca	gac	1059
														Thr		
PIIC	320	nıs	Deu	Gry	11.1.0	325	AL 9	DC u	115		330					
							. ~ ~ ~ •					2+01	- ~ ~ ~	~~~		1112
	tgas	gtca	ace c	ctcat	gac	ia Le	ageer	Laty	L Ca	cggci	Lycc	acci	-gcg			****
Arg																
335																
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															gggcag	
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caga	atgg	cac d	ctgt	ggcca	ag ag	gcac	ctca	g ga	ccct	cccc	acc	cacca	aaa	tgcc	tctgcc	1352
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															ttaagt	1472
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Tyr Val Ala Gly				
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aat gta tcc.ggt		=	= =	tct 398
Asn Val Ser Gly				
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gct ccc tta cag	ttc atg gct tct	gct ctc ttc a	atc tgg gct gct	cac 446
Ala Pro Leu Gln	Phe Met Ala Ser	Ala Leu Phe I	Ile Trp Ala Ala	His
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acc aac cgg aga				491
Thr Asn Arg Arg	Glu Tyr Thr Leu	Met Lys Ala T	Tyr Arg Val Ala	
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aactaaaaac tctat				
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ctctataaaa ttggg				
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aatacagtgt ttact				_
gaggattagt attat				
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aaagaacgtt tcacc			_	_
tctggctgtc catta				
ttccttgcct aaatc			_	
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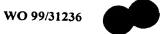
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-70 -65 -60 tgc cgg aag tac tac ctg ggg ggg ttt gct ttc ttg cct ttt ctc tgg	158
Cys Arg Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp -55 -50 -45	
ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala -40 -35 -30	206
tac aca gaa cag agc caa atc aaa ggc tat gtc tgg cgc tca gct gtg Tyr Thr Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val	254
-25 -20 -15 ggc ttc ctc ttc tgg gtg ata gtg ctc acc tcc tgg atc acc atc ttc	302
Gly Phe Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe -10 -5 1 5	
cag atc tac cgg ccc cgc tgg ggt gcc ctt ggg gac tac ctc tcc ttc Gln Ile Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe 10 15 20	350
10 15 20 acc ata ccc ctg ggc acc ccc tgacaacttc tgcacatact ggggccctgc .	401
Thr Ile Pro Leu Gly Thr Pro	
ttattctccc aggacaggct ccttaaagca gaggagcctg tcctgggagc cccttctcaa	461
actectaaga ettgttetea tgteecaegt tetetgetga catececeaa taaaggaeee.	521 542
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-50 -45 -40	

age ege aac eet gag gtg eee ttt gag age agt gee tae ege ate tea 145



Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser	
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gct tca gcc cgc ggc aag gag ctg cgc ctg ata ctg agc cct ctg cct Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro	193
-20 -15 -10 bet F10	
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Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly	
1 5 10	
atg tcc ggc tct ttt cag ctg gtg ccc cgc gag gag ctg cca cgc cat	289
Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His	
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Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu	
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Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 45 50 55 60	
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Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe	155
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Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro	
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Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn	
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Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 110 115 120	
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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro	025
125 130 135 140	
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Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp	
145 150 155	
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Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly	
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Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys	
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Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -65 -60 -65 -60 -65 -67			ים מר	יר ככ	יר מ	a ct	a ca	c ct	a ac	r ac	rc ca	a tt	t at	c aa	it gag	49
gcc tgc agg gcg ctg gtg ttc ggc ggc tgc gtg gag aaag tcc tct gtc Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -50 agc cgc aac cct gag gtg ccc ttt gag ag agc agt gcc tac cgc atc tca gc atc tca -35 -30 -25 -25 -30 -25 -25 -30 -25 -25 -30 -25 -25 -30 -25 -25 -30 -25 -25 -30 -35 -30 -25 -30 -25 -30 -35 -30 -35 -30 -25 -30 -25 -30 -30 -30 -30 -30 -30 -30 -30 -30 -30			lu Gl	y Pr				s Le	u Al				e Va	l As		
Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -50 -50 -65 -45 -46 -46 -47 -48 -40 -48 -40 -48 -40 -48 -40 -48 -40 -48 -40 -40 -48 -40 -40 -48 -40 -40 -40 -45 -40 -40 -46 -40 -46 -46 -46 -46 -46 -46 -46 -46 -46 -46	gcc tgc	agg	_	_	gtg	ttc	ggc	-	-	gtg	gag	aag	tcc	tct	gtc	97
Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser	Ala Cys	Arg	Ala	Leu	Val	Phe	Gly -45	Gly	Cys	Val	Glu	Lys -40	Ser	Ser	Val	
-15																145
Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -20	-35	5				-30					-25					102
-20																193
ggg gcc cag ccc caa cag gag cca ctg gcc ctg gtc ttc ggc ttc ggc ttc ggc 241 Gly Ala Gln Pro Gln Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 5 10 25 atg tcc ggc tct ttt cag ctg gtg ccc cgc gag gag ctg cca cgc cat Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Clu Leu Pro Arg His 15 25 289 gcc cac ctg cgc ttt tac acg gcc ccg cct ggc ccc cgg gtc cgc ccg ctg gag ccc cgg ctc gcc cta Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu Arg Pro Pro Gly Pro Arg Leu Ala Leu Arg Pro Pro Gly Pro Arg Leu Ala Leu Arg Pro Pro Gly Pro Arg Leu Gly Gly Lys Scr Lys Pro Cys Val Leu Gln Glu Tyr Gln Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Pro Gly Arg Gly Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala Pro Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Gln Ala Pro Arg Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile Pro Pro Pro Glu Leu Thr Leu Ser Gln Lys Ile Pro Pro Glu Leu Thr Leu Ser Gln Lys Ile Pro Pro Glu Leu Thr Leu Cys His Ser Val Leu Gln Ala Pro Arg Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 577 acg acg acg cac agg ccg agg ccg agg ccg agg cta ctg		. AIG	Arg	Gry		Giu	Беи	AT 9	Leu		100		110	Deu		
atg tcc ggc tct ttt cag ctg gtg ccc cgc gag gag ctg cca cat	ggg gcd															241
Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Clu Leu Pro Arg Glu Clu Pro Arg His 20 25 25 25 337 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Arg Leu Lya Ala Arg Leu Lya Ala Arg Leu Glu Lya	_			1				5					10			
gcc cac ctg cgc ttt tac acg gcc ccc ccc ccc ggc ccc cgg ctc ggc ccc cgg ctc ggc ccc add and his Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 30 35 40 40 40 50 55 60 50 50 50 50 50 50 50 50 50 50 50 50 50																289
Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 30 35 40 tgt ttc gtg gac atc cgc cgg ttc ggc cgc tgg gac ctt ggg gga aag Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 45 50 55 60 tgg cag ccg ggc cgc ggg ccc tgt gtc ttg cag gag tac cag cag ttc 65 70 70 75 agg ctg aag atc ccc ccc ttt gag aag gcc cgc tgg gtc ctg gag gcc Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg gag ctg ctg gag cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac aag ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ctg gag cta ctg ctg agc cag aag ata Leu Glu Ala 80 ctg cag cag cac agg ccg agc ctg agc ctg acc ctg agc cag aag ata 100 105 105 100 105 107 115 120 ccc aag gaa gtg gac cag ttg ggg ggc agg gcc tac ggg tca gag agc 125 130 135 140 ggg gag gag gag gac ttt gct gcc ttt cga gcc tgg ctg ctg ctg tac ggg 145 145 150 155 160 165 170 175 180 181 180 181 180 181 180 181 181 182 183 184 184 185 185 186 187 188 188		15					20					25				
tgt ttc gtg gac atc cgc cgg ttc ggc cgc tgg gac ctt ggg gga aag Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50																337
Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 45 50 50 55 60 tgg cag ccg ggc ccc ggg ccc tgt gtc ttg cag gag tac cag cag ttc Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 75 agg ctg aag atc ccc ccc ttt gag aag gcc cgc tcg gtc ctg gag gcc Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 95 agg acc aag ctg cag aat cca gac ctg ctg gag cta tgt cac tca gtg Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110 115 120 ccc aag gaa gtg gac cag ttg ggg ggc agg ggc tac ggg tca gag agc Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 125 130 130 135 atg cca ggc atg agc cct tcd cag gac ctg ctg ctg ctg ctg tat ggc Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 atg cca ggc atg agc cct ttg gaa cgc cad agc cgc cad acc atc tgg Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 165 170 180 aaa aag aaa tcc aag gcc aca cag ctg agc ccc aaa ggc cga aag tcc cgc Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Iys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu		ьLeu	Arg	Pne	Tyr		Ala	Pro	PIO	GIŸ		Arg	ьeu	Ala	Deu	
45 50 55 60 tgg cag ccg ggc ccg ggg ccc tgt gtc ttg cag gag tac cag cag ttc 433 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 75 agg ctg aag atc ccc ccc ttt gag aag gcc cgc tcg gtc ctg gag gcc 481 Arg Leu Lys Ile Pro Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala 80 85 90 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag aag ata 60 105 105 leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 95 100 105 agg acc aag ctg cag aat cca gac ctg gag ctg ctg gag cta tgt cac tca gtg Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110 115 120 ccc aag gaa gtg gac cag ttg gac cag ttg ggg ggc agg ggc tac ggg tca gag agc tca gag agc flu Ser 125 130 120 ccc aag gaa gag gac ttt tgct gcc ttt cga gcc tgg ctg ctg cgc tac gag agc flu Ser 125 130 125 ggg gag gag gac ttt gct gcc ttt cga gcc tgg ctg ctg ctg tat ggc flu Ser 125 140 ggg gag gag gac ttt gct gcc ttt cga gcc tgg ctg ctg ctg tat ggc flu Ser 140 150 ggg gag gag gac ttc gcc ttt cga gcc tgg ctg cac acc acc tgg flu Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 155 155 atg cca ggg gat ccc agg ccg agg ccc acc agg ccg agg ccg aagg cgc aagg																385
tgg cag ccg ggc cgc ggg ccc tgt gtc ttg cag gag tac cag cag ttc Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65	-	e Val	Asp	Ile	_	Arg	Phe	Gly	Arg	_	Asp	Leu	GIA	GIĀ		
Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 75 agg ctg aag atc ccc ccc ttt gag aag gcc cgc tcg gtc ctg gag gcc 481 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala 80 85 90 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aag ata 8529 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 105 agg acc aag ctg cag aat cca gac ctg gtg gag cta tgt cac tca gtg 577 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110 ccc aag gaa gtg gac cag ttg ggg ggc agg ggc tac ggg tca ggg agc 625 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 ggg gag gag gag gac ttt gct gcc ttt cga gcc tgg ctg cgc tgc tat ggc 673 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 atg cca ggg gat cct gga ccg acc acc ccg aag ggc cat agg cgc acc acc tcg gmet Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 ttc cag ggg gat cct agg ccc acc acc agg ccc aag ggc ccc aag tcg phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 aaa aag aaa tcc aag gcc aca cac cag ctg agt cct gag gac agg ggt gag gag gag gat scc agg gcc acc acc ccg gag acc acc agg aag acc ccg aag acc acc		cca	aac	cac		ccc	tat	atc	tta		aaa	tac	caq	caq		433
Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala 80 ctg cag cag cac agg ccg agc ccg gag ctg acc ctg agc cag aaa aag ata 529 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 95 aag acc aag ctg cag aat cca gac ctg ctg gag cta tgt cac tca gtg 577 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110 115 120 ccc aag gaa gtg gac cag ttg ggg ggc agg ggc tac ggg tca gag agc ccc aag agc ccc aag gag ggc agg ggc tac ggg tca gag agc 625 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 140 ggg gag gag gag gac ttt gct gcc ttt cga gcc tgg ctg cgc tgc tat ggc 673 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 155 atg cca ggg gat cct gga ccg ccg cad ggc cgc cad acc atc tgg 721 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 155 180 180 185 aaa aag aaa tcc aag gcc aca cac cag ctg agt ccc gag gac aga gtg gag gac ly ccc cac aca agg ccc ccc aaa ggc cgc aag tcc cgc 769 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 185 aaa aag aaa tcc aag gcc cac cac cag ctg agt cct gag gac aga gtg gag 817 Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu				Arg					Leu					Gln		
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Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 95 100 105 105 577 agg acc aag ctg cag aat cca gac ctg ctg gag cta tgt Leu Gln Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110 115 120 577 ccc aag gaa gtg gac cag ttg ggg ggc agg ggc tac ggg tca agg agc cca agg ggc tac ggg tca gag agc lea ggg ggg gag gag gag gac ttt ggc ly Arg Gly Tyr Gly Ser Glu Ser lat ggc ly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly lat ggc lat gag cca ggc tac ggc tac ggc tac ggc lat lat ggc lat ggc lat ggc cgt acc acc acc tac lat ggc lat lat ggc lat ggc lat ggc lat ggc lat ggc lat lat ggc lat ggc lat ggc lat ggc lat lat ggc lat ggc lat ggc lat ggc lat ggc lat lat ggc lat ggc lat ggc lat ggc lat ggc lat ggc lat		_	80					85.					90			
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Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 110		95					100					105				
110																577
Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 140 ggg gag gag gac ttt gct gcc ttt cga gcc tgg ctg cgc tgc tat ggc 673 674 673 673 674 673			ьеи	GIII	Asn		Asp	Leu	ъеп	GIU		Cys	uis	361	VAI	
125																625
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Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145		g gag	gac	ttt		gcc	ttt	cga	gcc		ctg	cgc	tgc	tat		673
Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 165 170 ttc cag ggg gat cct gga ccg ttg gca ccc aaa ggg cgc aag tcc cgc Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 185 aaa aag aaa tcc aag gcc aca cag ctg agt cct gag gac aga gtg gag Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu				Phe					Ala					Tyr		
ttc cag ggg gat cct gga ccg ttg gca ccc aaa ggg cgc aag tcc cgc Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 185 aaa aag aaa tcc aag gcc aca cag ctg agt cct gag gac aga gtg gag Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu																721
Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 185 aaa aag aaa tcc aag gcc aca cag ctg agt cct gag gac aga gtg gag Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu			160					165	_				170			
175 180 185 aaa aag aaa too aag goo aca cag otg agt oot gag gac aga gtg gag 817 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu																769
aaa aag aaa too aag goo aca cag otg agt oot gag gao aga gtg gag 817 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu	Pue GI	_	_	Pro	GIÀ	Pro		ATA	Pro	ьys	стĀ		тÀг	ser	Arg	
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			Ser	Lys	Ala		Gln	Leu	Ser	Pro		Asp	Arg	Val	Glu	



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Asp 205	Ala	Leu	Pro	Pro	210	гÀг	Ala	Pro	Ser	Lуs 215	THE	Arg	Arg	Ala	220	
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Arg	Asp	Leu	Pro	Lys	Arg	Thr	Ala	Thr		Arg	Pro	Glu	Gly	Thr	Ser	
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ctc	cag	cag	gac	cca	gaa	gct	CCC	aca	gtg	CCC	aag	aag	999	agg	agg	961
Leu	Gln	Gln	Asp	Pro	Glu	Ala	Pro	Thr	Val	Pro	Lys	Lys	Gly	Arg	Arg	
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Lys	Gly	Arg	Gln	Ala	Ala	Ser	Gly	His	Cys	Arg	Pro	Arg	Lys	Val	Lys	
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	Asp															
	270					275					280					
tage	cagga	agg (ctctc	cctt	gc tt	gcad	ctcad	cct	ttct	tat	tgto	cttg	ccc 1	tgcat	tctggg	1111
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cta	cacaa	act o	ctcat	gati	t ta	atte	gtaco	c cca	atct	cca	cato	ttta	aaa g	gctca	atgtga	1231
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Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly

atg tcc ggc tct ttt cag ctg gtg ccc cgc gag gag ctg cca cgc cat Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20

25

1

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WO 99/31236 PCT/IB98/02122 gee cae etg ege tit tae aeg gee eeg eet gge eee egg ete gee eta 337 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 tgt ttc gtg gac atc cgc cgg ttc ggc cgc tgg gac ctt ggg gga aag 385 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 tgg cag ccg ggc cgc ggg ccc tgt gtc ttg cag gag tac cag cag ttc 433 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe

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Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115 120 aag gcc cgc tcg gtc ctg gag gcc ctg cag cag cac agg ccg agc ccg 625 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro

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ggc aga ggc tac ggg tca gag agc ggg gag gac ttt gct gcc ttt 769 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 175 180

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			gcc Ala													152
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			cat His -10													296
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Asp	Ile 85	Ala	gaa Glu	Ser	Thr	Leu 90	Pro	Gly	Arg	His	Thr 95	gtt Val	Glu	Met	ctg Leu	584
			ttt Phe						tgaa	attat	ac d	ctaca	acct	g		631



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tac tat Tyr Tyr -200	tac Tyr	tcc Ser	aat Asn	ctc Leu -19	Ser	gtg Val	cct Pro	att Ile	999 Gly -190	Arg	ttc Phe	cag Gln	aac Asn	cgc Arg -185	205
gta cac Val His	Leu	Met	Gly -180	Asp)	Asn	Leu	Cys	Asn -17	Asp 5	Gly	Ser	Leu	Leu -170	Leu)	253
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cgt tac Arg Tyr	tac Tyr	cac His -85	aaa Lys	ctc Leu	agg Arg	atg Met	tct Ser -80	gcg Ala	gag Glu	tac Tyr	tcc Ser	cag Gln -75	agc Ser	tgg Trp	541
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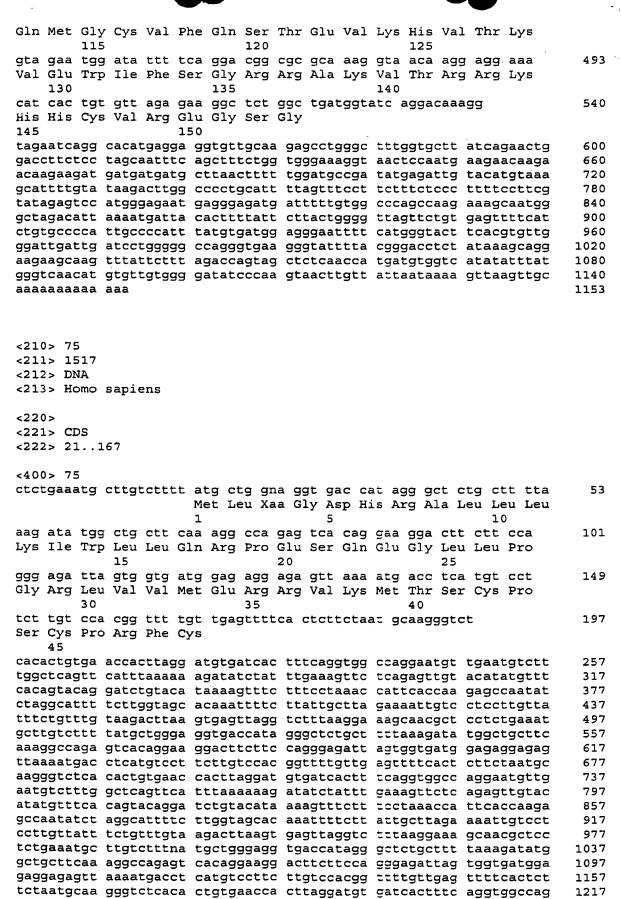
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gga Gly	att Ile 10	gtc_ Val	tgt Cys	gcc Ala	aca Thr	atc Ile 15	ctg Leu	ctg Leu	ctc Leu	cct Pro	gtc Val 20	ctg Leu	ata Ile	ttg Leu	atc Ile		829
Val 25	Lys	Lys	Thr	Cys	gga Gly 30	Asn	Lys	Ser	Ser	Val 35	Asn	Ser	aca Thr	gtc Val	ttg Leu 40	,	877
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Arg Phe Phe Ile Phe Cys Ser Leu Asn Thr Leu Leu Leu Gly Gly Val
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                                     -5
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Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Phe Val Phe Ser Gly Cys
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                                        45
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Asn Gly Asn Leu Asn Asn Phe Lys Leu Lys Ile Glu Arg Glu Val Ala
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Cys Val Ala Lys Tyr Lys Pro Pro Arg
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Lys	Pro	Val	Trp	Pro	Arg	Arg	Leu	Glu -15	Ser	Trp	Leu	Leu	Leu -10	Asp	Ala	
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		-5		-	_		1	_	•	_	5					
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				ctc												241
Pro	Pro	Pro	Cys	Leu	Gln	Gln	Pro	Asp		Arg	Ala	Leu	Ser		Ala	
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		_		ttt		_					_			_	_	289
Pne	Ser	Arg		Phe	Pro	Leu	Phe		Ser	Leu	Ala	GTA	_	Ser	Met	
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Cys Glu Thr Gly Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His 25 30 35	
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Lys Ile Gly Arg Gln Lys Leu Ala Lys Lys Met Phe Phe 90 95	
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att caa gta ttg aag atg ctg cca agg gaa aga tta aga aga aga gaa	155
Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Glu 20 25 30	
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Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu Thr 35	
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gag																256
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	agg Arg															147
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Ala Pro Gly Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala
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Glu Pro Leu Lys Thr Tyr Lys Met Gly Tyr
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Leu Ile Phe Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser -10 -5 1 5	
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Gly Val Arg Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu	
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Phe Gln Asp Thr Pro Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu	
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Gln Phe Phe Gln Lys Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val	
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Thr Leu Lys Gln Thr His Leu Asn Ser Gly Val Ile Leu Ser Ile His	400
75 80 85	
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Phe Cys Leu Arg Cys Thr Tyr Phe Pro Val His Cys Gly Met Cys Asn -35 -30 -25	
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Leu Arg Tyr Phe Glu Phe Ser Thr Phe Leu Leu Ser Leu Ile	

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tgg ttgg ttca	aagca attaa tataa attga aaaa attt	agt (aat (gaa (ccg (atg (cttt taga tgtt tata tcct ttca	aaaa ggtt aagt tgga gcca tgct	ac to	gctg gaaa aaga atgg taag attt	tgaaa aatco aagti ctgti ggtao	a car c aar t tar t cg c at	caggo ctcto cctto tgaco tgtag	ccat catc tgct attc gagc	cag ctg tta ttt	ggaa ggca ggtc atgt actt	gag gta gca tga	gaaa gttg agtt aatt gtta	tagttg tgctgc cctagt ccttat tgtgat ctgtgc taaagt	887 947 1007 1067 1127 1187 1247 1272
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	l> po	olyA 58	_sig		r CQS)	עעיי										
		olyA_ 93		3												
-400		_														
	38· <0	-			-~ ~	. ~ . ~ .			-~++					~-~-		60
ccaa	acac	cag g												tac a	acttga atg Met	60 116
ccaa agct	acaco acgcca att Ile	cag g aaa d	caagt caa	ctg	gt ag ctt	act Thr	aca	a ato	ccaga gat	aatg gat	gcti gga Gly	tgate att	caa	tac a	atg Met att	
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cac His gta Val -25 ctg Leu	att Ile -40 cat His gtc Val	tta Leu tgt Cys tgc Cys	caagt caa Gln cct Pro cat His	ctg Leu gac Asp gaa Glu -5 aca	ctt Leu act Thr -20 ttc Phe	act Thr -35 gga Gly tgc Cys	aca Thr aaa Lys cag Gln	gtg Val gac Asp tct Ser	gat Asp att Ile gat Asp 1	gat Asp tgg Trp -15 gat Asp	gga Gly -30 aat Asn cca Pro	att Ile tta Leu ccc Pro	caa Gln ctt Leu atc Ile 5	gca Ala ttt Phe	atg Met att Ile gac Asp -10 ctt Leu gcc	116 164 212
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ccas agct cac His gta Val -25 ctg Leu caa Gln atc Ile gat Asp 40 cag Gln	acacca att Ile -40 cat His gtc Val gaa Glu tat Tyr 25 ctt Leu tgt Cys aaa	tta teu tgt Cys tgc Cys cag Gln 10 gca Ala cct Pro	caagt caa Gln cct Pro cat His aaa Lys tca cta Leu aaa Lys	ctg Leu gac Asp gaa -5 aca Thr cag Gln att Ile aaa Lys gat	cttu acttr-20ce Phe gtgl actr Actr Actr Actr Accr Accr Accr Accr A	act Thr -35 gga Gly tgc Cys cta Leu gag Glu 30 agc Ser gag Glu acc	aca Thr aaa Lys cag Gln gcc Ala 15 caa Gln ctc Leu aac Asn	gtg Val gac Asp tct Ser tct Ser tct gag Glu att Ile tcg sat	gat Asp atte gatp I tat Tyr cgg Arg Ala 65 gat	gat Asp tggTrp-15 gat Asp ttt Phe ctau gtc Val gag Glu ctc	ggtt gga Gly -30 aat Asn cca Pro tca Ser aag Lys 35 tta Leu tct Ser	att Ile ttau CCO gtgl 20 atle Caa Gln aac Asn	caa Gln ctt Leu atc 5 ttg Leu gaa Glu aat Asn aca Thr	gca Ala ttt Phe att Ile tct aaa Lys atg Glu 70 atc	atg Met att Ile gac Asp -10 ctt Leu gcc Ala gtal Val gaa Glu 55 gaa Glu tta	116 164 212 260 308 356 404
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Lys	Glu 105	Thr	Val	Ala	Gln	Gly	Val	Lys	Glu	Gly	Gln 115	Leu	Ser	Lys	Gln	590
Lys 120	Cys	Ser	Ser	gca Ala	Phe 125	Gln	Asn	Leu	Leu	Pro 130	Phe	Tyr	Ser	Pro	Val 135	644
Val	Glu	Asp	Phe	att Ile 140	Lys	Ile	Leu	Arg	Glu 145	Val	Asp	Lys	Ala	ctt Leu 150	gct Ala	692
				aaa Lys										<u>-</u>		734

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Leu	Lys	Glu	Lys	Phe	Arg	Thr	Met	Glu	Ser	Asn	Gln	Lys	Ser	Ser	Phe		
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Gln	Glu	Ile	Pro	Lys	Leu	Asn	Glu	Glu	Leu	Leu	Ser	Lys	Gln	Lys	Gln		
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Pro	Thr	Thr	Val	Glu	Gly	Leu	Gln	Lys	Ser	Val	Ala	Ser	Ile	Gly	Asn		
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Thr	Leu	Asn	Ser	Val	His	Leu	Ala	Val	Glu	Ala	Leu	Gln	Lys	Thr	Val		
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His Phe Leu Lys Glu Thr Pro Gly Ser Asn Gln Ile Ile Pro S 140 145 150 tca gcc aca tca gaa ctt gac aat aaa acc cac agt gag aat t Ser Ala Thr Ser Glu Leu Asp Asn Lys Thr His Ser Glu Asn I 160 165 1 cag atg ggt gat aga tct gcc act ctg aaa aga cag tct ttg g Gln Met Gly Asp Arg Ser Ala Thr Leu Lys Arg Gln Ser Leu A 175 180 185 gtc acc aac aga aca gat aca gta aaa atc caa aaa aaa aaa a Val Thr Asn Arg Thr Asp Thr Val Lys Ile Gln Lys Lys	s	is :	Lys	Lys	Thr		Glu	Leu	Leu	Gln		Asp	Met	Asn	Gln	
Ser Ala Thr Ser Glu Leu Asp Asn Lys Thr His Ser Glu Asn I 160 165 1 cag atg ggt gat aga tct gcc act ctg aaa aga cag tct ttg g Gln Met Gly Asp Arg Ser Ala Thr Leu Lys Arg Gln Ser Leu A 175 180 185 gtc acc aac aga aca gat aca gta aaa atc caa aaa aaa aa a Val Thr Asn Arg Thr Asp Thr Val Lys Ile Gln Lys Lys	_	_	_		Thr			_		Gln			_			663
Gln Met Gly Asp Arg Ser Ala Thr Leu Lys Arg Gln Ser Leu A 175 180 185 gtc acc aac aga aca gat aca gta aaa atc caa aaa aaa aa a Val Thr Asn Arg Thr Asp Thr Val Lys Ile Gln Lys Lys				Glu		_			Thr		_			_		711
Val Thr Asn Arg Thr Asp Thr Val Lys Ile Gln Lys Lys		īy i	Asp	_		_		Leu		_	_		Leu	-		759
170	n	sn i	_		_		_							a		802

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4		
•	•	,,

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Trp	Met	Leu	Ala	Leu	Leu	Gly	Leu	Ser	Gln	Āla	Leu	Asn	Ile	Leu	Leu		
			85					90		•			95				
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Gly	Leu			Leu	Ala	Pro	Ala	Glu	Ile	Ser	Ala	Val	Cys	Glu	Lys		
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999	aat	ttc	aac	gtg	gcc	cat	999	ctg	gca	tgg	tca	tat	tac	atc	gga	· 5	35
GIA	Asn	Phe	Asn	Val	Ala		Gly	Leu	Ala	${\tt Trp}$	Ser	Tyr	Tyr	Ile	Gly		
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Tat	ctg	cgg	ctg	atc	ctg	cca	gag	ctc	cag	gcc	cgg	att	cga	act	tac	5	83
120	ьeu	Arg	Leu	TTe		Pro	Glu	Leu	Gln		Arg	Ile	Arg	Thr	_		
130			.		135					140					145		
Aac Acn	Cag	Uic	Tac	aac	aac	ctg	cta	cgg	ggt	gca	gtg	agc	cag	cgg	ctg	6	31
ASII	GIII	uis	TAT	150	ASI	теп	Leu	Arg	Gly	Ala	Val	Ser	GIn		Leu		
+=+	2++	ata	ata						155					160		_	
Tur	Tle	Len	Len	Dro	Leg	gac	Cur	999	gtg	CCL	gat	aac	ctg	agt	atg	6	79
171	110	шец	165	PIQ	ьец	Asp	Cys	170	Val	PIO	Asp	ASD		ser	Met		
act	gac	CCC		a++	cac	++0	ata		aaa				175			_	
Ala	Asp	Pro	Asn	Tle	Ara	Dhe	Leu) cn	Lys	Lou	D=0	cag	cag	acc	ggt	7	27
	· · · · ·	180	71011		Yr A	FIIC	185	Asp	пур	пеп	PIO		GIII	THE	GIA		
gac	cat		gac	atc	aag	gat		att	tac	200	226	190	5 t c		~~~	-	~ -
Asp	Ara	Ala	Glv	Tle	Lvs	Asp	Ara	Val	Tyr	Ser	Aac Aan	Sor	Tla	Tree	Gag	,	75
	195		1		_, _	200	9	V 44 1	- y -	DCI	205	261	116	ıyı	GIU		
ctt		qaq	aac	aaa	cag		aca	aac	acc	tat		cta	a a a	tac	~~~	0	23
Leu	Leu	Glu	Asn	Glv	Gln	Ara	Ala	Glv	Thr	Cvs	Val	Len	Glu	Tyr	Δla	0.	23
210				2	215	5		,		220	· u ·	DC u	GIU	TYT	225		
acc	ccc	ttg	caq	act	tta	ttt	acc	ato	tca		tac	agt	caa	act	aac	8	71
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cag	gag	gtt	CTC	cgg	cac	ctg	cgg	cag	gag	gaa	aag	gaa	gag	gtt	acc	106	53
290	GIU	vaı	ьeu	Arg		Leu	Arg	Gin	Glu		Lys	Glu	Glu	Val			
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Val	Glv	age Ser	LLG	aag	acc	Com	gcg	gtg	CCC	agt	acc	tcc	acg	atg	tcc	111	L1
vai	Gly	261		195 310	Inr	ser	Ата	vaı	Pro	Ser	Thr	Ser	Thr		Ser		
caa	aaa	cct			ctc	a+a	~~+	~~-	315					320			
Gln	Glu	Dro	Glu	T.en	Leu	Len	agt Cor	gga Clu	atg Met	99a	aag	CCC	CTC	CCT	CTC	115	9
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Arg	Thr	Asp	Phe	Ser	cgag	accc	ag g	yıca	ccag	g cc	agag	CCEC	cag	tggt	CTC	121	.4
3		340		201													
caao			acto	aaaa	c to	t.c++	cant	acc	tass	+ ~+	~~~	c=~-	ac +		aa++-	127	. 4
caca	adaa	מכ כ	ttar	agan	a ac	aatr	cada	350	tasa	atr	ttas	caya cate	90- C	a	tcccc	127	
ttgg	gcca	gt c	attt	-222	t ct	ctaa	acat	Cau	tato	ttc	2200	yaly tata	eg t	taaa	atcat	133 139	
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cgc					cgg					tta				atg Met 40	tct	148
				tct					tgg					gtc Val		196
			cag					ctg					cca	tcc Ser		244
acg Thr	tca Ser 75	gct	tca Ser	gcc Ala	cta Leu	gat Asp 80	caa	ccc Pro	tca Ser	ttt Phe	gtt Val 85	ccc	aaa Lys	tct Ser	cct Pro	292
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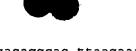
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Asn Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys

35

591



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atcgcttgaa	cttgggaggc	ggaggttgca	gtgagcctag	attttgccat	tgcactccag	561
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ctc atc cca tct atg ctg tca agg gct gct ggt tgg tgc tgg tac aag
                                                                      101
Leu Ile Pro Ser Met Leu Ser Arg Ala Ala Gly Trp Cys Trp Tyr Lys
                - 5
gag ecc act cag cag tit tet tac ett tge etg ecc tge ett tea tgg
                                                                      149
Glu Pro Thr Gln Gln Phe Ser Tyr Leu Cys Leu Pro Cys Leu Ser Trp
                            15
                                                20
ast asg asa ggc asc gtt ttg cag ctt cca ast ttc tgasgasact
                                                                      195
Asn Lys Lys Gly Asn Val Leu Gln Leu Pro Asn Phe
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ttggctaccc ggttcaattg ctttttattt ttaatgtctt gactcttcag agttcgtacc
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tcaaaagaac aatgagaaca tttgctttgc tttctgctga atccctaatc tcaacaatct
                                                                      375
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Met	Glu	Arg	Gly	Leu	Lys	Ser	Ala	Asp	Pro	Arg	Asp	Gly	Thr	Gly	Tyr	
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act	aac	tgg	gca	ggt	att	gct	gtg	ctt	tac	tta	cat	ctt	tat	gat	gta	153
Thr	Gly	Trp		Gly	Ile	Ala	Val	Leu	Tyr	Leu	His	Leu	Tyr	Asp	Val	
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Pne	GIA	Asp	Pro	Ala	Tyr	Leu	Gln	Leu	Ala	His	Gly	Tyr	Val	Lys	Gln	
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ser	ren	Asn	Cys	Leu		Lys	Arg	Ser	Ile		Phe	Leu	Cys	Gly	_	
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AId	GIY	Pro	Leu	Ala	Val	Ala	Ala	Val		Tyr	His	Lys	Met		Asn	
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Giu	цуѕ	GIII	A1a	Glu	Asp	Cys	тте		Arg	Leu	Ile	His		Asn	Lys	
2++	~ a t	00t						55					60			
Tle	Acn	Dro	Tio	gct	Dwa	aat	gaa	atg	CEC	tat	999	cga	ata	ggc	tac	393
	ASD	65	uis	Ala	PIO	ASI	70	Mer	Leu	Tyr	GIY		Ile	Gly	Tyr	
atc	tat		a++	a++	+++	ata	. •					75				
Tle	Tyr	Ala	Len	ctt	Dho	gue	Aac Nam	aag	aac	בננ	gga	ará	gaa	aag	act	441
	80	AIA	пец	Leu	Pile	85	ASII	ьуs	Asn	Pne		val	GIu	ьуs	Tnr	
cat		acc	cat	att	C2C		a++	+~+	~~~		90					
Pro	Gln	Ser	His	Ile	Cln	Gla	Tla	Cyc	gaa	The	Tlo	tta	acc	CCL	gga	489
95			*****		100	GIII	116	Cys	GIU	105	TTE	Leu	Inr	ser		
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Glu	Asn	Lev	Ala	Arg	Live	Ara	Acr	Dhe	Thr	yca N1-	Tuc	CO.	Dro	Tor	arg	537
				115	-75	9	47011	THE	120	MIG	пåа	3e1	PIO		Met	
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					Leu											
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Ile	Gln	Ala	Tyr 210	Lys	Val	Phe	Arg	Glu 215	Glu	Lys	Tyr	Leu	Cys 220	Asp	Ala	
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Tyr	Gln	Cys 225	Ala	Asp	Val	Ile	Trp 230	Gln	Tyr	Gly	Leu	Leu 235	Lys	Lys	Gly	
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Tyr	Gly 240	Leu	Cys	His	Gly	Ser 245	Ala	Gly	Asn	Ala	Tyr 250	Ala	Phe	Leu	Thr	
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	Tyr	Asn	Leu	Thr	Gln	Asp	Met	Lys	Tyr		Tyr	Arg	Ala	Cys	-	
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Phe	Ala	GIU	Trp	Cys 275	Leu	GIU	Tyr	GIY	280	His	GIÀ	Cys	Arg	7nr 285	Pro	
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						Me	t Gl:	n Met	t As	Th:	r Ph	e Ph	e Met	t Ser	
						1				5					
gaa aaa															401
Glu Lys	His	Thr	His	Thr	His	Thr	His	Ile	His	Thr	His	Thr	Arg	Lys	
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Thr Lys	Lys	Lys	Lys												
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tcc tcc ggg cac ctt cct nntgaaggag tggctaaggt tggacaatac Ser Ser Gly His Leu Pro 50	193
acgttcactg cagctgctgt cggggccgtg tttggcctca ccacctgcat cagcgccat gtccgcgaga agcccgacga ccccctgaac tacttccccg gtggctgcgc cnggaggcct gactctggga gcacgcacgc acaactacgg gattggcgcc gccgcctgcg tgtactttgg catagcggcc tccctggtca agatgggccg gctggagggc tgggaggtgt ttgcaaaacc caaggtgtga gccctgtgcc tgccgggacc tccagcctgc agaatgcgtc cagaaataaa ttctgtgtct gtgtgtaaa aaaaaaaaa	253 313 373 433 493 522
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gcg gca gtg gcg cct gtc ctg tcc ata aac agc gat ttc tca gat ttg Ala Ala Val Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu -5	99
cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	147
cgg ggc cta cta cac agt agc aaa tgg tcg gcg gag ttg gct ttc tct	195





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25					30			Trp		35					40		
ctc Leu	cct Pro	gca Ala	ttg Leu	cct Pro 45	cnt Xaa	ggc Gly	cag Gln	ctg Leu	caa Gln 50	ccg	cct Pro	ccg Pro	cct Pro	att Ile 55	aca		243
gag Glu	gaa Glu	gat Asp	gcc Ala 60	cag	gat Asp	atg Met	gat Asp	gcc Ala 65	tat	acc Thr	ctg Leu	gcc Ala	aag Lys 70	gcc	tac Tyr	2	291
ttt Phe	gac Asp	gtt Val 75	aaa	gag Glu	tat Tyr	gat Asp	cgg Arg 80	gca Ala	gca Ala	cat His	ttc Phe	ctg Leu 85	cat	Gly	tgc Cys	3	339
aat Asn	agc Ser 90	aag Lys	aaa Lys	gcc Ala	tat Tyr	ttt Phe 95	ctg Leu	tat Tyr	atg Met	tat Tyr	tcc Ser 100	aga	tat Tyr	ctg Leu	gtg Val	3	887——
agg Arg 105	gcc Ala	att Ile	tta Leu	aaa Lys	tgt Cys 110	cat His	tct Ser	gcc Ala	ttt Phe	agt Ser 115	gaa Glu	aca Thr	tcc Ser	ata Ile	ttt Phe 120	4	35
aga Arg	acc Thr	aat Asn	gga Gly	aaa Lys 125	gtt Val	aaa Lys	tct Ser	ttt Phe	aaa Lys 130	tago	ttag	jca g	jtgg <u>g</u>	gccac	et	4	85
gaat	gaat	gt a	cttt	atac	a ta	acaa	taat	: aaa	aaaa	aga	tato	ataa	at a	aaat	taaaa	5	45
agga	tagt	ag a	gaac	aaaa	t at	tctt	agga	ato	acta	aca	ggat	aaat			tgatt	6	05
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atta	tgaa	tt t	actt	tcct	a ct	tttt	ctta	gtt	gtta	tct	atat	aaat	tq a	ttaa	aaaaa	9	05
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			Àla													
	100			-		105	_				110		_	-		
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			Thr													
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-			•	135			-		140	•				145		
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			Gly													
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gac	gag	qac	cca	qcc	acc	aqc	acc	caa	caa	ccc	tac	cag		cca	ata	628
			Pro													
•		165					170	5	5		-1-	175				
tcc	qtq	atq	ccc	atc	acc	acc		gac	caa	gaa	aac		agc	agc	ttt	676
Ser	Val	Met	Pro	Val	Ãla	Thr	Ser	Asp	Gln	Glu	Glv	Asp	Ser	Ser	Phe	
	180					185					190					
ggc	aaa	tac	ggc	aga	aac		tac	ata	tage	aget		acco	atac	aa		723
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195	•	- 3 -	2		200		- 2 -									
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tctt	gcac	tc	tcato	gcc	c to	cago	ccaa	gaa	ctq	tct	tgac	gaaqt	cg c	atat	ctccc	903
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gaa ata ata Glu Ile Ile	tcc ttg aa Ser Leu Ly -40	a gag gaa tca s Glu Glu Ser -35	Pro Leu G	gga aag gtg agt cag Gly Lys Val Ser Gln -30	162
Gly Pro Leu -25	Phe Asn Va	l Thr Ser Gly -20	Ser Ser S	ca cca gtg acc tgg er Pro Val Thr Trp -15	210
Leu Gly Leu	ctc tcc ttc Leu Ser Pho	e Gln Asn Leu	His Cys P	tc cca gac ctc ccc he Pro Asp Leu Pro	258
-10 act gag atg Thr Glu Met	cct cta aga Pro Leu Ara 10	-5 a gcc aaa gga g Ala Lys Gly	1 gtc aac ac Val Asn Tl 15	ct tgagcctagg	304
cttgctgaag tatttttgtt	acaaaagatt q gaacttaaaa q gaatcgaaac q taaattccgc q	agtagctgtt at aattccatgt ag	gcttcatc to ttattgta to caatcttt to	aggtccagg ccccaagtag tgtataagc taaaaacatt ttctgttca cggtgtttgt atgggaatt gaccggatag	364 424 484 544 558

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Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu 80 85 90	
ctc aag gat ggt cag cag att cct gtg ttc aag ctc agt ggg gaa aac	497
Leu Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn	
95 100 105	548
ggt gat gaa gtg aaa aag gag tagagacgac ccagaagacc cagcttgctt Gly Asp Glu Val Lys Lys Glu 110 115	240
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Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser	
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Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His	
20 25 30	
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Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro	
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Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu	
65 70 75	
ctg gag gtg gac gat tgg gag ttc tgagcctctg caaactgtgc gcattctcca	356
Leu Glu Val Asp Asp Trp Glu Phe	
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Met Arg Thr	170
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Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr Leu Leu Leu	
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atc acc cct tet ecc age cet ett eta ttt gat aga ggt etg tee etc	274
Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly Leu Ser Leu	
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Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg Leu Cys Glu Arg Asp Val	= - =
10 15 20	
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Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser Asp Leu Lys Arg Ile Asn

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Gly Phe															
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tac aac	aga	gtg	cct	tta	cac	aaa	cct	acg	gat	tgg	cag	aaa	aag	atc	245
Tyr Asn	Arg	Val	Pro		His	Lys	Pro	Thr	_	Trp	Gln	Lys	Lys		
55				60					65					70	
ctc ata				_			_		_						293
Leu Ile	Trp	Ser	_	Arg	Phe	Lys	Lys		Asp	Glu	Ile	Pro		Thr	
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gtc tcg	_		_				-	_							341
Val Ser	Leu		Met	Leu	Asp	Ala		Lys	Asn	Lys	Met		Val	Lys	
		90					95					100			
agc agc															389
Ser Ser	_	Leu	Met.	Ile	Ala		Thr	Val	Val	Gly	_	Ile	Phe	Met	
	105					110					115				
gtt att															437
Val Ile		Gly	Lys	Lys		Ala	Gln	Arg	His		Thr	Leu	Thr	Ser	
120					125					130					
ttg aac		-	_		_	_	_			_	_	_	_	-	485
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Ala Lys															
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			1	Met '	Val (Cys (Glu 1	Lys (Cys (Glu 1	Lys 1	Lys :	Leu (Gly	
				1			!	5					10		
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Thr Val	Ile	Thr	Pro	Asp	Thr	Trp	Lys	Asp	Gly	Ala	Arg	Asn	Thr	Thr	
		15.					20					25			
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Glu Ser	Gly	Gly	Arg	Lys	Leu	Asn	Lys	Asn	Lys	Ala	Leu	Thr	Ser	Lys	
	30	-	_	_		35	_		_		40			_	
aaa gca	aga	ttt	gat	cca	tat	gga	aag	aat	aag	ttc	tcc	act	tgt	aga	194
Lys Ala	_		_				_		_				_	-	
45	_		-		50	_	-		-	55			-	-	
att tgt	aaa	agt	tct	gtq	cac	caa	cca	ggt	tct	cat	tac	tgc	cag	ggc	242
Ile Cys															
-								-			-	-		_	
60				65					70					75	

tgt gcc tac aaa aaa ggc atc tgt gcg atg tgt ggn aaa aaa gtt ttg

493



Cys Ala Tyr Lys Lys Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu 80 85 90	
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Asp Thr Lys Asn Tyr Lys Gln Thr Ser Val	
95 100	
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cagaataaca tgttttaaga taattaagtt taaaccagag aatttgattg ttactcat	tt 460
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gta gaa agg aag aaa tgc cac aaa cag gct ctt gtt ggc agt gac

Val Glu Arg Lys Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp 90 95 100 tct gct gaa gat gag aaa aga agg aaa tgc cag aaa cat gcc cct

Ser Ala Glu Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro

110

105



•	•															
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	Asn	Ser	Ala	Gln		Leu	Asp	Asn	Val	_	Gln	Thr	Gly	Pro		
120					125					130					135	500
-		-		_		aca Thr					_		-			589
		_, _	01,	140					145		<i></i> , .	· · · ·		150	027	
						cct										637
Ser	Thr	Ser		Lys	Pro	Pro	His		Leu	Ser	Arg	Lys		Trp	Arg	
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Gln		Pro	Asp	Gln	Ala	Pro	Ala	Glu	Ala	Pro		Glu	Lys	Thr	Glu	
~+~	185					190					195					701
						aca Thr										781
200			,		205					210		•••		1	215	
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Leu	Arg	Ala	Arg		Ala	Gln	Arg	Leu	Asp	Gly	Ala	Arg	Phe	Arg	Tyr	
				220					225					230		
						tca Ser										877
neu	M311	GIU.	235	Deu	TYL	261	Gly	240	SEI	ser	AIA	MIG	245	Arg	пеп	
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		250					255		٠			260				
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ser	265	vaı	тув	гàг	Trp	Pro 270	гел	GIN	Pro	val	275	Arg	11e	Ala	Arg	
gat		cac	cag	caa	cct	gca	tac	cta	ata	ata		gac	ttc	aac	tat	1021
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_						tca										1069
GIA	Asp	Cys	Arg		Ala	Ser	Ser	Ile	_	Asn	Pro	Val	His	_	Phe	:
gac	tta	act	tct	300	as c	cct	200	atc	305	ata	+~+	~ = ~	a t ~	310	cac	1117
						Pro										,
-			315		•		_	320				•	325			
						tct										1165
Val	Pro		Glu	Asp	Glu	Ser		Asp	Val	Ala	Val		Cys	Leu	Ser	
cta	ato	330	200	220	250	agg	335	++6	a t 2	~~~	~~~	340	-	202	at a	1213
						Arg										1213
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	Lys	Pro	Gly	Gly		Leu	Lys	Val	Ala		Val	Ser	Ser	Arg		
360	~~+				365					370					375	1200
						ctg Leu										1309
OIU	rap	vai	Arg	380	FIIE	neu	Arg	AIA	385	TIII	пÃг	neu	GIY	390	пур	
att	gtc	tcc	aag		ctg	acc	aac	agc	•	ttc	ttc	ttg	ttt		ttc	1357
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			395					400					405			
						ctg										1405
GIII	пуs	410	GIY	PIO	PIO	Leu	415	GIY	PIO	гÀг	Ala	420	ьeu	ser	GIŞ	
ctg	cag		caq	cca	tat	ctc		aaq	cac	agg	tgad	-	aa a	atctt	ccttg	1458
						Leu					5		55 -		3	
	425				_	430		_	_	_						
															ctggc	1518
rati	₃ agc	aa 9	jacct	-ggt1	c ct	ggt	gaco	ctg	gagga	ıcaa	agto	grgat	aa a	acct	ctggc	1578



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458

494

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acteactatg gaatetgact ggacacettg getatttgta aggggttatt tttattatga gaattaattg ccttgtttat gtacagattt tctgtagcct taaaggaaaa aaaaataaag

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<213> Homo sapiens

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gct gct ttc tcc gtc ctc ccc tgt tac tac ctt ggg ctg ttt cag cgg Ala Ala Phe Ser Val Leu Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg -15 -10 -5	161
gcg ctc gcg tcg gtc ttc gac cca ctt tgc gtt tgt tca cgt gtg ctc Ala Leu Ala Ser Val Phe Asp Pro Leu Cys Val Cys Ser Arg Val Leu 1 5 10	209
ccg aca cct gta tgt acc ttg gtc gca aca caa gcc gaa aaa ata tta Pro Thr Pro Val Cys Thr Leu Val Ala Thr Gln Ala Glu Lys Ile Leu 15 20 25	257
gag aat ggg ccc tgt cca acc aag gag gcg gcc cag ctt gtc ggg aag Glu Asn Gly Pro Cys Pro Thr Lys Glu Ala Ala Gln Leu Val Gly Lys 30 35 40 45	305
ggc agc gtt tcc gcc aga aat gct tcg tgaaaggcac ttgagggacc Gly Ser Val Ser Ala Arg Asn Ala Ser 50	352
ttagcagcat cctcaacagg ccttgtaggg aatgccagaa gaagcagtcc ttggccgggc ggggtggctc atgcctgtgg tcccagcact ttgggaggcc ggggcgggcg gatcacctga ggtcgggagg tccagaccag cctgaccgac atggagaaac cccgtctnta ctagaaatac aaaactagcc gggtgtggtg gcgcatgcct gtagtcccag ctactcggga gggtgaggca ggagacgttc ttgaacccgg gaggcggagt ttgtggtgag ccgagatcgc gccattgcac tccagcctgg gcatgccaag agcgaaactc cgtctcaaaa aaaaaaaaaa	412 472 532 592 652 712
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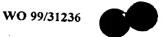
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ccc ttc ccc gtg ctc ctt ctg gcc gct ctg cct ccg gtg ctg c	100
ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt acc Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr 1 5 10 15	148
ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg aag Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu Lys	196
gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta gat Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu Asp 35 40 45	244
att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt gaa Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe Glu 50 55 60	292
caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt gat Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp 65 70 75 80	340
tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag gtg Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val 85 90 95	388
att ttc ttt gaa tta atc ctg gat aat atg gga gaa cag gca caa gaa Ile Phe Phe Glu Leu Ile Leu Asp Asn Met Gly Glu Gln Ala Gln Glu 100 105 110	436
caa gaa gat tgg aag aaa tat att act ggc aca gat ata ttg gat atg Gln Glu Asp Trp Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp Met 115 120 125	484
aaa ctg gaa gac atc ctg gaa tcc atc agc agc atc aag tcc aga cta Lys Leu Glu Asp Ile Leu Glu Ser Ile Ser Ser Ile Lys Ser Arg Leu 130 135 140	532
agc aaa agt ggg cac ata caa att ctg ctt aga gca ttt gaa gct cgt Ser Lys Ser Gly His Ile Gln Ile Leu Leu Arg Ala Phe Glu Ala Arg 145 150 155 160	580
gat cga aac ata caa gaa agc aac ttt gat aga gtc aat ttc tgg tct Asp Arg Asn Ile Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser 165 170 175	628
atg gtt aat tta gtg gtc atg gtg gtg gtg tca gcc att caa gtt tat Met Val Asn Leu Val Val Met Val Val Val Ser Ala Ile Gln Val Tyr 180 185 190	676
atg ctg aag agt ctg ttt gaa gat aag agg aaa agt aga act Met Leu Lys Ser Leu Phe Glu Asp Lys Arg Lys Ser Arg Thr 195 200 205	718
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<210> 111

<211> 787

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 26..481

<221> sig_peptide

<222> 26..88

<223> Von Heijne matrix



score 4.4 seq AVASSFFCASLFS/AV

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<221> polyA_site <222> 775..787

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gtg gct tcc agt ttc ttt tgt Val Ala Ser Ser Phe Phe Cys -10	_		100
ata gaa gag gga cat att ggg Ile Glu Glu Gly His Ile Gly 5 10			148
act tcg acc agc ggc cct ggt Thr Ser Thr Ser Gly Pro Gly 25	_		196
tca tat aag tct gtg cag acc Ser Tyr Lys Ser Val Gln Thr 40			244
gta cct tgt ggg act agt ggt Val Pro Cys Gly Thr Ser Gly 55			292
gaa gtg gtg aac ttc ctg gtc Glu Val Val Asn Phe Leu Val 70 75			340
aac tat act gct gac tat gac Asn Tyr Thr Ala Asp Tyr Asp 85 90	J J	_	388
cac gaa ctg aac cag ttc tgc His Glu Leu Asn Gln Phe Cys 105			436
att gag ctg ttt gga ctg gaa Ile Glu Leu Phe Gly Leu Glu 120	•	2 0	481
taaaagggac cctgagcaag aacatt	tttc atagcagaca		541
cagcaatcat aattaagcaa accgcc			601
attactttta atgtttctgc agtaga	aaat gaatctaaat	tcattttata gggtttgtag	661
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<211> 569

<212> DNA

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<220>

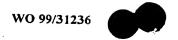
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<222> 26..562

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<222> 26..187

<223> Von Heijne matrix score 4.1





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Ser -45	Ser	ccg Pro	Ser	Leu	Lys -40	Thr	Asp	Thr	Ser	Pro -35	Val	Leu	Glu	Thr	Ala -30	100
gga Gly	acg Thr	gtc Val	gca Ala	Ala	atg Met	gct Ala	gcg Ala	acc Thr	Pro	tca Ser	gca Ala	agg Arg	gct Ala	Ala	gcc Ala	 148
				-25					-20					-15		
Ala	Val	gtt Val	Ala -10	Ala	Ala	Ala	Arg	Thr -5	Gly	Ser	Glu	Ala	Arg 1	Val	Ser	196
Lys	Ala 5	gct Ala	Leu	Ala	Thr	Lys 10	Leu	Leu	Ser	Leu	Ser 15	Gly	Val	Phe	Ala	244
Val 20	His	aag Lys	Pro	Lys	Gly 25	Pro	Thr	Ser	Ala	Glu 30	Leu	Leu	Asn	Arg	Leu 35	292
Lys	Glu	aag Lys	Leu	Leu 40	Ala	Glu	Ala	Gly	Met 45	Pro	Ser	Pro	Glu	Trp 50	Thr	340
Lys	Arg	aaa Lys	Lys 55	Gln	Thr	Leu	Lys	Ile 60	Gly	His	Gly	Gly	Thr 65	Leu	Asp	388
Ser	Ala	gcc Ala 70	Arg	Gly	Val	Leu	Val 75	Val	Gly	Ile	Gly	Ser 80	Gly	Thr	Lys	436
Met	Leu 85	acc Thr	Ser	Met	Leu	Ser	Gly	Ser	Lys	Arg	Tyr 95	Thr	Ala	Ile	Gly	484
Glu 100	Leu	Gly 999	Lys	Ala	Thr 105	Asp	Thr	Leu	Asp	Ser 110	Thr	Gly ggg	aag Lys	gta Val	aca Thr 115	532
gaa Glu	gaa Glu	aaa Lys	cct Pro	tac Tyr 120	ggt Gly	atg Met	aac Asn	ctc Leu	atc Ile 125	taag	tag					569

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<211> 893

<212> DNA

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<222> 4..810

<221> sig_peptide

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<221> polyA_signal

<222> 858..863

<221> polyA_site

<222> 881..893



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ctg ctt gaa gag ctt ccc ctc ccc gac cag cag cca tgc atc gag cct	96
Leu Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro	,
-75 -70 -65	744
cca cct tcc tcc atc atg tac cag gct aac ttt gac aca aac ttt gag	144
Pro Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu	
-60 -55 -50	
gac agg aat gca ttt gtc acg ggc att gca agg tac att gag cag gct	192
Asp Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala	
-4 5 -4 0 -3 5 -3 0	
aca gtc cac tcc agc atg aat gag atg ctg gag gaa gga cat gag tat	240
Thr Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr	
-25 -20 -15	
gcg gtc atg ctg tac acc tgg cgc agc tgt tcc cgg gcc att ccc cag	288
Ala Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln	
-10 -5 1	
gtg aaa tgc aac gag cag ccc aac cga gta gag atc tat gag aag aca	336
Val Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr	330
5 10 15	204
gta gag gtg ctg gag ccg gag gtc acc aag ctc atg aag ttc atg tat	384
Val Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr	
20 25 30 35	
ttt cag cgc aag gcc atc gag cgg ttc tgc agc gag gtg aag cgg ctg	432
Phe Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu	
40 45 50	
tgc cat gcc gag cgc agg aag gac ttt gtc tct gag gcc tac ctc ctg	480
Cys His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu	
55 60 65	
acc ctt ggc aag ttc atc aac atg ttt gct gtc ctg gat gag cta aag	528
Thr Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys	
70 75 80	
aac atg aag tgc agc gtc aag aat gac cac tcc gcc tac aag agg gca	576
Asn Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala	
85 90 95	
	624
gca cag ttc ctg cgg aag atg gca gat ccc cag tct atc cag gag tcg	024
Ala Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser	
100 105 110 115	670
cag aac ett tee atg tte etg gee aac eac aac agg ate ace eag tgt	672
Gln Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys	
120 125 130	
ctc cac cag caa ctt gaa gtg atc cca ggc tat gag gag ctg ctg gct	720
Leu His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala	
135 140 145	
gac att gtc aac atc tgt gtg gat tac tac gag aac aag atg tac ctg	768
Asp Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu	
150 155 160	
act ccc agt gag aaa cat atg ctc ctc aag gta aaa ctc ccc	810
Thr Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro	_
165 170 175	
tgaggccgca cccatggagc ctgggcttac cctctcacct tcttcttatt aaaaatccgt	870
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<213> Homo sapiens

1269

1329

1389



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1475

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Asp Ala Ala Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn -25 -20 -15 agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta agt Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Ser -10 -5 1 aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat tac Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr 5 10 ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu	
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Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu	243
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Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys 40 45 50	339
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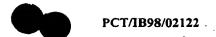
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Asp Phe Leu Arg Ser Leu Ser Asp Gly Asp Ser Gly Thr Ser Glu His
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Ile Pro Thr Ala Arg Ala Leu Cys Leu Gly Cys Ser Cys Cys Thr Glu
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Arg Leu Leu Pro Pro Pro Ser Leu Leu Ser Leu Glu Ala Pro Ala
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Ser Thr
80
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Ala	Ile	Glu	Pro 145		Trp	His	Ala	Gln 150	Val	Gln	Ala	Val	Phe 155	Leu	Pro		
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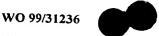
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175





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<213> Homo sapiens

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<222> 816..821

<221> polyA_site

<222> 840..853



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Phe	Val	Ile	Ala	Cys	Val	Leu	Ser	Leu	Ile	Ser	Thr	Ile 1	Tyr	Met	Ala	
gcc	tcc	att	ggc	aca	gac	ttc	tgg	tat	gaa	tat	cga	agt	cca	gtt	caa	150
Ala	Ser	Ile	Gly	Thr	Asp	Phe	Trp	Tyr	Glu	Tyr	Arg	Ser	Pro	Val	Gin 20	
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gaa	aat	tcc	agt	gat	ttg	aat	aaa	agc	TIA	Trn	yar Nen	Glu	-Phe-	att Tle	Ser	
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gat	gaa	gca	gat	gaa	aag	act	tat	aat	gat	gca	cct	בלכ	cga	tac	aat Aan	246
			40					45					50	Tyr		
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Gly	Thr	Val	Gly	Leu	$\mathtt{Trp}$	Arg	Arg	Cys	Ile	Thr	Ile	Pro	Lys	Asn	Met	
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cat	tgg	tat	agc	cca	cca	gaa	agg	aca	gag	Com	מלכ	gat	gra	gtc	Thr	342
His		Tyr	Ser	Pro	Pro	75	Arg	THE	GIU	Ser	80	Asp	VOI	Val	1111	
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Lvs	Cvs	Val	Ser	Phe	Thr	Leu	Thr	Glu	Gln	Phe	Met	Glu	Lys	Phe	Val	
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Asp	Pro	Gly	Asn	His	Asn	Ser	Gly	Ile	Asp	Leu	Leu	Arg	Thr	Tyr	Leu	
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Trp	Arg	Cys		Phe	Leu	Leu	Pro	125	vaı	Ser	Leu	GIY	130	Met	Cys	
		+	120	- <b>-</b> -	~~~	a++	+~+		tac	att	tac	cga		tta	tat	534
The	999	712	T.An	Tle	994 617	Lèn	Cvs	Ala	Cvs	Ile	Cvs	Ara	Ser	Leu	Tyr	
		135					140					145				582
CCC	acc	att	gcc	acg	ggc	att	ctc	cat	ctc	ctt	gca	gat	acc	atg	ctg	562
Pro	Thr 150	Ile	Ala	Thr	Gly	11e	Leu	Hls	Leu	Leu	160	Asp	THE	Met	nea	
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ccg tgt gcc cat gag gcc ctc ctg gac gag gac acc ctc ttt tgc cag Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln 10 15 20	146										
ggc ctt gaa gtt ttc tac cca gag ttg ggg aac att ggc tgc aag gtt Gly Leu Glu Val Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val 25 30 35	194										
gtt cct gat tgt aac aac tac aga cag aag atc acc tcc tgg atg gag Val Pro Asp Cys Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu 40 45 50	242										
ccg ata gtc aag ttc ccg ggg gcc gtg gac ggc gca acc tat atc ctg Pro Ile Val Lys Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu 55 60 65 70	290										
gtg atg gtg gat cca gat gcc cct agc aga gca gaa ccc aga cag aga Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg 75 80 85	338										
ttc tgg aga cat tgg ctg gta aca gat atc aag ggc gcc gac ctg aag Phe Trp Arg His Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys 90 95 100	386										
aaa ggg aag att cag ggc cag gag tta tca gcc tac cag gct ccc tcc Lys Gly Lys Ile Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser 105 110 115	434										
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ggc tct tgg aaa atg gac aga ttt ctg aac cgt ttc cac ctg ggc gaa Gly Ser Trp Lys Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu 155 160 165	578										
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cgg ctc ctc tac atc ggc ttc ttg ggc tac tgc tcc ggc ctg att gat Arg Leu Leu Tyr Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp -10 -5 1	205												
aac ctg atc cgg cgg agg ccg atc gcg acg gct ggt ttg cat cgc cag Asn Leu Ile Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln 5 10 15	253												
Ctt cta tat att acg gcc ttt ttt ttg ctg gat att atc ttg Leu Leu Tyr Ile Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu 20 25 30	295												
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tacatecaga ggatttteet gaagaagata agaaaacata tqqtqaaatt tttqaaaaat	415												
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<210> 126

<211> 659

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<222> 601..606

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aga Arg	att Ile	gtg Val 30	gcc Ala	ata Ile	aag Lys	aag Lys	ttc Phe 35	tta Leu	gaa Glu	agt Ser	gac	gat Asp 40	gac Asp	aaa Lys	atg Met	568
gtt Val	aaa Lys 45	aag Lys	att Ile	gca Ala	atg Met	cga Arg 50	gaa Glu	gtc Val	aag Lys	tta Leu	cta Leu 55	aag Lys	caa Gln	ctt Leu	agg Arg	616
cat His 60	gaa Glu	aac Asn	ttg Leu	gtg Val	aat Asn 65	ctc Leu	ttg Leu	gaa Glu	gtg Val	tgt Cys 70	aaa Lys	aaa Lys	aaa Lys	a		659

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Phe Gly Asn Leu Phe Leu Cys Val Gln Phe Val Arg Glu Lys Gln Ser	247												
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gcc tct gag gct gcg tgc ctg atc gtg tct gta gat gaa acc atc aag 97

Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys
20 25 30

aac ccc cgc tcg act gtg gat gct ccc aca gca gca ggc cgg ggc cgt 145



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ggt	cgt	ggc	cgc	CCC	cac	tgag	gagge	cac .	ccca	ccat	c ac	catgo	ctg	g ·			193
Gly	Arg 50	ĞÎy	Arg	Pro	His				•				_	_			
ctg	ctgo	etg d	gtac	actt	acc	ctc	cttg	g ct	tggti	tact	tcat	ttta	ca	aggaa	aggg	gt	253
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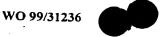
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205

253

301

349



20

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gac tgg act ctg tca cca gga gag cac gcc aag gac gaa tat gtg cta	157

caa gat gtg caa gag gct gac cag gga acc tat atc tgt gaa atc cgc Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 70 ctc aaa ggg gag agc cag gtg ttc aag aag gcg gtg gta ctg cat gtg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val

55

Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu

Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg _____45_____45____ gta cac ttg atg ggg gac atc tta tgc aat gat ggc tct ctc ctg ctc

Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu

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90

60





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Leu Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys	216
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gacettettg atg ctg get gtt tet ete ace gtt eee etg ett gga gee	169
Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu Gly Ala	
-10 -5	
atg atg ctg ctg gaa tct cct ata gat cca cag cct ctc agc ttc aaa	217
met met Leu Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys	
na al-mark toward is a law March of historia and of the broad and all the allowing and all the law towards and a company of the allowing the company of the	
gaa ccc ccg ctc ttg ctt ggt gtt ctg cat cca aat acg aag ctg cga Glu Pro Pro Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg	265
20	
Cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag tcc ata	212
Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile	313
35 40 45	
gca cat att ggg gat gtg atg ttt act ggg aca gca gat ggg cgg otc	361
Ala his lie Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val	301
50 55 60	



PCT/IB98/02122 -

gta	aaa	ctt	gaa	aat	ggt	gaa	ata	gag	acc	att	gcc	cgg	ttt	ggt	tcg		409
	Lys	Leu	Glu	Asn		Glu	Ile	Glu	Thr	Ile	Ala	Arg	Phe	Gly	Ser		
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GIY	Pro	Cys	Lys	Thr	Arg	qaA	Asp	Glu		Val	Cys	Gly	Arg		Leu		
				85					90					95			
ggt	atc	cgt	gca	aaa	CCC	aat	999	act	ctc	ttt	gtg	gcc	gat	gca	tgc	į	505
GIA	тте	Arg		Gly	Pro	Asn	GIA		Leu	Phe	Val	Ala		Ala	Cys		
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гур	Gī	115	PHE	Glu	vai	AŞN		Trp	гув	Arg	GIU		гàг	Leu	Leu		
cta	tcc		~~~	300			120					125					
T.em	Ser	Ser	Glu	aca Thr	Dro	Tla	Clu	999	aag	aac	acg	Com	מלם	gtg	aat	(	601
шси	130	361	GIU	T T T T	PLO	135	GIU	GIY	тув	ASII	140	Ser	Pne	vaı	ASI		
gat		aca	atc	tct	cad		aaa	200	224	a++		++~	200	~~+		,	<b>540</b>
Asp	Leu	Thr	Val	Ser	Gla	Acn	61 v	Arg	Lve	Tla	Tur	Dhe	Th~	yac Nen	202	,	549
145					150	App	Oly	A. 9	Lys	155	TYL	FIIC	1111	Asp	160		
	agc	aaa	taa	caa		cga	gac	tac	cta		cta	ata	ata	<b>a</b> aa			597
Ser	Ser	Lvs	Trp	Gln	Ara	Ara	Asp	Tvr	Len	Len	T.en	Val	Met	Glu	Glv	,	391
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Thr	Asp	Asp	Gly	Arg	Leu	Leu	Glu	Tyr	Asp	Thr	Val	Thr	Arq	Glu	Val		
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Lys	Val	Leu	Leu	Asp	Gln	Leu	Arg	Phe	Pro	Asn	Gly	Val	Gln	Leu	Ser		
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Pro		Glu	Asp	Phe	Val	Leu	Val	Ala	Glu	Thr	Thr	Met	Ala	Arg	Ile		
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cga	aga	gtc	tac	gtt	tct	ggc	ctg	atg	aag	ggc	999	gct	gat	ctg	ttt	ε	889
Arg	Arg	Val	Tyr	Val		Gly	Leu	Met	Lys		Gly	Ala	Asp	Leu	Phe		
225					230					235					240		
grg	gag	aac	atg	cct	gga	ttt	cca	gac	aac	atc	cgg	ccc	agc	agc	tct	9	37
vaı	GIu	Asn	Met	Pro	Gly	Phe	Pro	Asp		Ile	Arg	Pro	Ser		Ser		
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GIY	GIA	Tyr		Val	GIA	Met	Ser		lle	Arg	Pro	Asn		Gly	Phe		
+	- t-a		260					265					270				
Ser	Met	Leu	yar Nan	ttc	LLd	Com	gag	aga	200	rgg	att	aaa	agg	atg	att	10	33
261	C	275	vah	Phe	חבת	2CT	280	Arg	PIO	пр	тте		AIG	Met	тте		
ttt	aad	_	222	aaa	222	22	200					285					\E->
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                                                                       112
                             Met Phe Ala Pro Ala Val Met Arg Ala
                                      -30
                                                         -25
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                                                                       160
 Phe Arg Lys Asn Lys Thr Leu Gly Tyr Gly Val Pro Met Leu Leu
             -20
                                 -15
att gtt gga ggt tct ttt ggt ctt cgt gag ttt tct caa atc cga tat
                                                                      208
Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
gat gct gtg aag agt aaa atg gat cct gag ctt gaa aaa aaa ctg aaa
                                                                      256
Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
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                                         20
gag aat aaa ata tct tta gag tcg gaa tat gag aaa atc aaa gac tcc
                                                                      304
Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser
                 30
aag ttt gat gac tgg aag aat att cga gga ccc agg cct tgg gaa gat
                                                                      352
Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
            45
                                 50
cct gac ctc ctc caa gga aga aat cca gaa agc ctt aag act aag aca
                                                                      400
Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr
                             65
act tgactctgct gattcttttt tccnnntttt ttttttttta aataaaaata
                                                                      453
Thr
ctattaactg gacttcctaa tatatacttc tatcaagtgg aaaggaaatt ccaggcccat
                                                                      513
ggaaacttgg atatgggtaa tttgatgaca aataatcttc actaaaggtc atgtacaggt
                                                                      573
ttttatactt cccagctatt ccatctgtgg atgaaagtaa caatgttggc cacgtatatt
                                                                      633
ttacacctcg aaataaaaaa tgtgaatact gctccaaaaa aaaaaaccag taccgtgtag
                                                                      693
tctctctcgt ggcttggatt tacactgggc aacgtggttg gaatgtatct ggctcagaac
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<223> Von Heijne matrix
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sexp LMCLSLCTAFALS/KP

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gaa aag aag gac cgt gta cat cat gag cct cag ctc agt gac aag gtt Glu Lys Lys Asp Arg Val His His Glu Pro Gln Leu Ser Asp Lys Val 5 10 15	150
cac aat gat att tgatagaacc aattgttgta cataaaacag atctgcgcat His Asn Asp Ile 20	202
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gcc tcc att ggc aca gac ttc tgg tat gaa tat cga agt cca gtt caa Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 5 10 15 20	150
gaa aat too agt gat ttg aat aaa ago ato tgg gat gaa tto att agt	198
Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35	130
gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn 40 45 50	246
ggc aca gtg gga ttg tgg gga cgg tgt atc acc ata ccc aaa aac atg Gly Thr Val Gly Leu Trp Gly Arg Cys Ile Thr Ile Pro Lys Asn Met	294
55 60 65 cat tgg tat agc cca cca gaa agg aca ggt att tct ctt att tta act	240
His Trp Tyr Ser Pro Pro Glu Arg Thr Gly Ile Ser Leu Ile Leu Thr	342



70	75	80	
tot gto tto tto acc tgg	tta ata ata gac aaa	acg acg taatgattgc	391
Ser Val Phe Phe Thr Trp	Leu Ile Ile Asp Lys	Thr Thr	
85 90	95		
ccaattacat gtaagcaggt tt	gttggttc tctctcct	taaagaaata aatcgtgtat	451
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ttggttggat gaggaacttt to	ttatcttg ggaaagcctt	aatggctttt ttttttctta	571
tttactcact cattaaaata ct	tttcatta ctctaacaca	tgttataaag aaatagttgg	631
aaaagtgcat cgaaagactt tt	aaaaatat ttggtaacta	gtaaaaggac taccatcgaa	691
aatcaactca aaaaattgtc ct	tttatggg ttagctgtat	tataatacat atctatcatt	751
tgcccctgtg tcttagagga ta	taatttga ccagctctac	atttaatctg tgtaattatg	811
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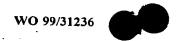
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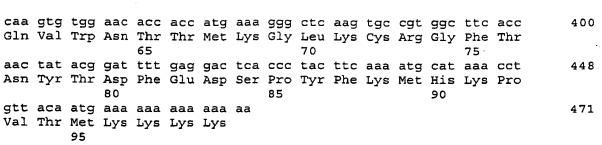
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			Met -30					-25					-20			
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		-15	Leu				-10					-5				
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	1		Leu		5					10					15	
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GIY	Gly	Ala	Met	Val 20	Tyr	Gly	Leu	Ile	Met 25	Gly	Leu	Ile	Ser	Arg 30	Tyr	
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Ala	Thr	Ala	Pro 35	Thr	Asp	Ile	Glu	Ser 40	Gly	Thr	Val	Cys	Asp 45	Cys	Val	
aaa	cta	act	ttc	agt	cca	cca	act	ctg	ctg	gtt	aat	gtc	act	gac	caa	345
Lys	Leu	Thr	Phe	Ser	Pro	Pro	Thr	Leu	Leu	Val	Asn	Val	Thr	Asp	Gln	
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Val	Tyr 65	Glu	Tyr	Lys	Tyr	Lys 70	Arg	Glu	Ile	Ser	Gln 75	His	Asn	Ile	Asn	
cct	cat	caa	gga	aat	gct	ata	ctt	gaa	aag	atg	aca	ttt	gat	cca	qaa	441
Pro 80	His	Gln	Gly	Asn	Ala 85	Ile	Leu	Glu	Lys	Met 90	Thr	Phe	Asp	Pro	Glu 95	
atc	ttc	ttc	aat	gtt	tta	ctg	cca	cca	att	ata	ttt	cat	gca	gga	tat	489
Ile	Phe	Phe	Asn	Val 100	Leu	Leu	Pro	Pro	Ile 105	Ile	Phe	His	Ala	Gly 110	Tyr	





agt cta aag aag aga cac ttt ttt caa aac tta gga tct att tta acg Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly Ser Ile Leu Thr 115 120 125	537
tat gcc ttc ttg gga act gcc atc tcc tgc atc gtc ata ggg Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val Ile Gly 130 135 140	579
taagtgacat teggagetea agttgeaggt ggetgtgggg tetgtgatet gtgtgaggga tetaacactt ceaggattet tgetggetgg gaaaattgte tttttttag tatateacat atttgtatgt tttttetgae ttaatteeae ggettetgae aaataeaagg etteaaatea aageaaacta gaggattget ggaetttete tgtgagttet ggaettetga ettaaggaat gtggateaet tgeettgagt tatgtgaage geattgeatt	639 699 759 819 879 939 1059 1119 1239 1244
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tac ttc ctc atc gca gcc ggc gtt gtg gtc ctt gct ctt ggt ttc ctg Tyr Phe Leu Ile Ala Ala Gly Val Val Leu Ala Leu Gly Phe Leu -20 -15 -10 -5	160
ggc tgc tat ggt gct aag act gag agc atg tgt gcc ctc gtg acg ttc Gly Cys Tyr Gly Ala Lys Thr Glu Ser Met Cys Ala Leu Val Thr Phe 1 5 10	208
Phe Phe Ile Leu Leu Leu Ile Phe Ile Ala Glu Val Ala Ala Val 15 20 25	256
yal Ala Leu Val Tyr Thr Thr Met Ala Glu His Phe Leu Thr Leu Leu 30 35 40	304
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Tyr Gln Leu Tyr Ser Leu Leu Arg Ser Glu Lys Trp Asn His Thr Leu



5					10					15					20	
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Ser	Met	Ala	Leu	Ile 25	Leu	Phe	Cys	Asn	Tyr 30	Tyr	Val	Leu	Phe	Lys 35	Leu	
ctc	cgg	gac	a.ga	ata	gta	tta	ggc	agg	gca	tac	tcc	tac	cca	ctc	aac	654
Leu	Arg	Asp	Arg	Ile	Val	Leu	Gly	Arg	Ala	Tyr	Ser	Tyr	Pro	Leu	Asn	
			40					45		-			50			
agt	tat	gaa	ctc	aag	gca	aac	taag	gctgd	cct d	ctcaa	acaat	g ag	ggag	gaact	<u>:</u>	705
Ser	Tyr	Glu	Leu	Lys	Ala	Asn										
		55														
caga	taaa	laa t	tattt	tcat	a co	ttct	attt	: ttt	tctt	gtg	attt	ttat	aa a	atatt	taaga	765
gtt	ttat	at t	tttgt	atac	ct at	tate	gtttt	: gaa	aagto	ggg	aaga	agtaa	agg g	gatat	taaat	825
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 Ala
 Asp
 Phe
 Tyr
 Lys
 Glu
 Phe
 Leu
 Ser
 Lys
 Asn
 Phe
 Gln
 Lys
 Arg

 Met
 Tyr
 Tyr
 Asn
 Arg
 Asn
 Tyr
 Tyr
 Lys
 Arg
 Asn
 Phe
 Ala
 Ile
 Thr
 Phe

 Phe
 Met
 Gly
 Lys
 Val
 Ala
 Leu
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Thr Ala Ala Leu Pro Ala

Met Pro Val Pro Ala Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr -15 Arg Pro Ala Ser Ala Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala 20 Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Trp Leu Thr Lys Ala Arg 35 Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu 50 Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 70 Glu Thr Gln Met Glu Glu Asp Ile Leu Gln Leu Gln Ala Glu Ala Thr 85 Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100 95 Ser Val Gln Arg Leu Glu Val Gln Leu Arg Ser Ala Trp Leu Gly Pro 120 115 Ala Tyr Arg Glu Phe Glu Val Leu Lys Ala His Ala Asp Lys Gln Ser 130 His Ile Leu Trp Ala Leu Thr Gly His Val Gln Arg Gln Arg Glu 150 145 Met Val Ala Gln Gln His Arg Leu Arg Gln Ile Gln Glu Arg Leu His 160

<210> 145

175

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<211> 135
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
Met Ser Leu Arg Asn Leu Trp Arg Asp Tyr Lys Val Leu Val Val Met
                    -20
                                         -15
Val Pro Leu Val Gly Leu Ile His Leu Gly Trp Tyr Arg Ile Lys Ser
                - 5
Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro Glu Gln Asp
       10
                            15
Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                    45
                                        50
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
                                     65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
                                80
Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln Ser Gln Ser
                            95
Lys Gln Lys Ser Ile Glu Glu
<210> 146
<211> 255
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -70..-1
<400> 146
Met Gln Gln Lys Glu Gln Gln Phe Arg Glu Trp Phe Leu Lys Glu Phe
                    -65
                                         -60
Pro Gln Ile Arg Trp Lys Ile Gln Glu Ser Ile Glu Arg Leu Arg Val
                -50
Ile Ala Asn Glu Ile Glu Lys Val His Arg Gly Cys Val Ile Ala Asn
            -35
                                -30
Val Val Ser Gly Ser Thr Gly Ile Leu Ser Val Ile Gly Val Met Leu
                            -15
                                                -10
```

Ala Pro Phe Thr Ala Gly Leu Ser Leu Ser Ile Thr Ala Ala Gly Val

Gly Leu Gly Ile Ala Ser Ala Thr Ala Gly Ile Ala Ser Ser Ile Val

Glu Asn Thr Tyr Thr Arg Ser Ala Glu Leu Thr Ala Ser Arg Leu Thr

35 Ala Thr Ser Thr Asp Gln Leu Glu Ala Leu Arg Asp Ile Leu His Asp 50 Ile Thr Pro Asn Val Leu Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr

20

15

30



60 65 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 85 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 95 100 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 115 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 130 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 145 150 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 160 165 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 175

<210> 147
<211> 59
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -49..-1

<210> 148 <211> 180 <212> PRT <213> Homo sapiens

Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys Asp His Gln Leu 10 Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser Gln Leu Ser Ala 40 Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr Gly Ser Arg His .....50_____60____ Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu Tyr Leu Glu Thr Lys 70 Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser Leu Ser Ser Thr Gly Thr 85 90 Phe Leu Val Asp Asn Ser Ser Val Asp Phe Gln Lys Phe Pro Asp Lys 100 105 Glu Ile Leu Arg Met Ala Gly Pro Leu Thr Ala Asp Phe Ile Val Lys 120 Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr Val Gln Phe Ile Phe Tyr

<210> 149

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<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 149
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Ala Ala
           -20
                               -15
Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
       - 5
Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
                  15
                                       20
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
                                  35
              30
Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
                              50
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
                   95
                                       100
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
              110
                                  115
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met
                              130
Val Phe
```

Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val

20

35

15

30

<210> 150



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Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
45 50 55

Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
60 65 70

Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn
75 80 85

Pro Ser Thr Phe Arg Gly Gln Val
90 95
```

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<210> 151
<211> 7
<212> PRT
<213> Homo sapiens
<400> 151
Met Val Glu Met Thr Gly Val
<210> 152
<211> 199
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 152
Met Asp Gly Gln Lys Lys Asn Trp Lys Asp Lys Val Val Asp Leu Leu
                            -35
                                                -30
Tyr Trp Arg Asp Ile Lys Lys Thr Gly Val Val Phe Gly Ala Ser Leu
                        -20
                                            -15
Phe Leu Leu Ser Leu Thr Val Phe Ser Ile Val Ser Val Thr Ala
                    - 5
                                        1
Tyr Ile Ala Leu Ala Leu Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr
            10
                                15
Lys Gly Val Ile Gln Ala Ile Gln Lys Ser Asp Glu Gly His Pro Phe
                            30
Arg Ala Tyr Leu Glu Ser Glu Val Ala Ile Ser Glu Glu Leu Val Gln
                       45
Lys Tyr Ser Asn Ser Ala Leu Gly His Val Asn Cys Thr Ile Lys Glu
                   60
Leu Arg Arg Leu Phe Leu Val Asp Asp Leu Val Asp Ser Leu Lys Phe
                75
                                    80
Ala Val Leu Met Trp Val Phe Thr Tyr Val Gly Ala Leu Phe Asn Gly
           90 .
                                95
                                                    100
Leu Thr Leu Leu Ile Leu Ala Leu Ile Ser Leu Phe Ser Val Pro Val
                            110
                                                115
Ile Tyr Glu Arg His Gln Ala Gln Ile Asp His Tyr Leu Val Leu Ala
                       125
                                            130
Asn Lys Asn Val Lys Asp Ala Met Ala Lys Ile Gln Ala Lys Ile Pro
                   140
                                        145
Gly Leu Lys Arg Lys Ala Glu
```

<210> 153

155

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<211> 43
<212> PRT
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<213> Homo sapiens

<400> 153

Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys 25 Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp

40

<210> 154

<211> 50

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 154

Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro -35 -30 -25

Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe -15

Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala

Gln Glu

<210> 155

<211> 153

<212> PRT

<213> Homo sapiens

<400> 155

Thr Val Pro Leu Leu Glu Pro Ala Asp His Ala Arg Gly Arg Ala 10

His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val 25

Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu 40 4.5

Lys Glm Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu 55

Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr 70 75

Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser 85 90

Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys 105

Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly 120 125

Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro 135

Gln Val Ser Gln Gln Glu Glu Leu Lys

150



<210> 156 <211> 67 <212> PRT

<213> Homo sapiens

<400> 156

Met Arg Gln Lys Arg Lys Gly Asp Leu Ser Pro Ala Lys Leu Met Met 1 5 10 15 Leu Thr Ile Gly Asp Val Ile Lys Gln Leu Ile Glu Ala His Glu Gln

20 25 30

Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys 35 40 45

Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val 50 55 60

Pro Pro Glu

65

<210> 157

<211> 87

<212> PRT

<213> Homo sapiens

<400> 157

Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val Ser Arg Ala Arg

1 5 10 15

Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val Phe

Lys lie Gin Arg Phe Leu Ser Gin Pro Phe Gin Val Ala Glu Val Phe
20
25
30

Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
35
40
45

Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
50 55 60

Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp Lys 65 70 75 80

Leu Ala Glu Glu His Ser Ser

85

<210> 158

<211> 250

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -85..-1

<400> 158

Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe Leu

_-85 ______-70 _____-70 Leu Leu Ala Lys Gly Ala Ala Leu Ala Thr Leu Ile His

-65 -60 -55
Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp

-50 -45 -40 Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr

-35 -30 -25
Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
-20 -15

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Glu Ala Leu Ala

-5 Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr 15 20 Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala 50 Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 65 70 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln 85 Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 100 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Thr Ser Gln 115 120 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 130 135 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 145 150 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn 160

<210> 159

<211> 24

<212> PRT

<213> Homo sapiens

<400> 159

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys

1 10 15

His Ile Asn Ile Ser Phe His Arg
20

<210> 160

<211> 228

<212> PRT

<213> Homo sapiens

<400> 160

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 25 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 40 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 70 75 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 135 140 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg



145 150 155 Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu 165 170 Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro 180 185 Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln 200 205 Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys 215 Ser Thr Phe Ile 225

بالك وهوا ووالم المناول والمواليات والمنافية والمنافية والمنافي أواليها والمنافلات والمنافية والمنافرة والمنافرة

<210 > 163 <211 > 314 <212 > PRT <213 > Homo sapiens <220 > <221 > SIGNAL <222 > -58..-1

<210> 162

<400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -55 -50 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -35 -30 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -15 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 10 15 Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 30 Ile Ile Glu Glu Asp Asp Gly Asp Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 60 65 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 75 80 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp 125 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 140 145 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 155 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 170 175 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro 190 195 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 220 225 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 240 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met 250

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -80..-1

-45 -40 -35 Leu Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr

```
-30 -25 -20

Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
-15 -10 -5

Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
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<210> 165 <211> 98 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -15..-1

<400> 165

Thr Ala

<220>

 Met
 Glu
 Ala
 Met
 Trp
 Leu
 Leu
 Cys
 Val
 Ala
 Leu
 Ala
 Val
 Leu
 Ala
 Trp

 Gly
 Phe
 Leu
 Trp
 Val
 Trp
 Asp
 Ser
 Ser
 Glu
 Arg
 Met
 Lys
 Ser
 Arg
 Glu
 Arg
 Arg

<210 > 166 <211 > 92 <212 > PRT <213 > Homo sapiens <220 > <221 > SIGNAL <222 > -36..-1

<210> 167
<211> 351
<212> PRT

<213> Homo sapiens

WO 99/31236

<220>

<221> SIGNAL

<222> -16..-1

<400> 167

Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10

Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10

Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile

Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40

Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 55

Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 70 75

Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 85 90

Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 100 105

Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 120

Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135

Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155

Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 165 170

Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 180 185

Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 200 205

Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220

Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 230

235 Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp

245 250 Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser

260 265 - 270 Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 275 280 285

Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys 295

300 His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys

310 315

His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg 330

<210> 168

<211> 138

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -47..-1

<210> 169 <211> 101



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<400> 168
Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu
                            -40
                                                -35
Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser
                        -25
Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile
                    -10
Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu
Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile
       20
                           25
Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu
                                            45
Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe
                    55
                                        60
Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu
                                    75
Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala
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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -73..-1
<400> 169
Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg
                                -65
Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val
        -55
                            -50
Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr
                        -35
                                            -30
Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe
                    -20
                                        -15
Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile
                                    1
Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile
       10
Pro Leu Gly Thr Pro
   25
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Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -50 -45 -40 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 15 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 60 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115 120 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys 180

<210> 171 <211> 350 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

<400> 171 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu

-60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 -50 -40 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 65 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala



80 85 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 100 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 115 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 165 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 180 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 195 200 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 210 215 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 240 245 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 260 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

<210> 172 <211> 390 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1 <400> 172

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 40 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu

115

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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 160 165 170 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 175 180 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 200 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 210 215 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 225 230 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 240 245 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 260 265 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 295 290 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 310 305 Glu Gly Thr Ser Ala Ser 320

<210> 173
<211> 190
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL

<222> -82..-1

<400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -25 -30 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -10 - 5 -15 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 40 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 75 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85 90 Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

95 100 105

<210> 174 <211> 285 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -232..-1

<400> 174 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile -230 -225 -220 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu -215 -210 -205 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg -200 -195 -190 Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu -180 -175 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg -165 -160 -155 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val -150 -145 -140 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile -130 -125 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys -115 -110 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe -100 - 95 -90 Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp -80 Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn -65 Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn -50 -45 Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile -35 -30 Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala -20 -15 Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val 1 Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile 15 20 Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu 30 35 Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys 4.5

<210> 175

<211> 153

<212> PRT

<213> Homo sapiens

<400> 175

Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 10 15 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu



20 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 40 35 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 105 110 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1

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-133-
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<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
        -35
                            -30
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
                                20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
                           35
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
```

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<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Phe Leu Leu Phe Phe Phe
                                -15
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
Gln Lys Leu Ala Lys Lys Met Phe Phe
```

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<210> 180
<211> 59
<212> PRT
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<213> Homo sapiens

<400> 180

<210> 179

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

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1 5 10 15

Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg 20 25 30

Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu 35 40 45

Thr Pro Arg Lys Arg Glu Gly Lys Lys Lys Lys 50 55
```

<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 <400> 182

70

Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -55 -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -5 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 15 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 Ser Leu Gln Asp Ala Leu Leu Leu Leu Met Gly Leu Gly Pro Leu <210> 183

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<211> 80
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -35..-1
  <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
                   -30
                                     -25
. Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ala Ala
                  -15
                                     -10
  Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
 Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
                         20
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Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys

40

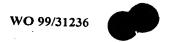
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<210> 184
<211> 73
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -21..-1
<400> 184
Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
                        -15
Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
                                20
Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                           35
                                                40
Cys Gly Asn Ile Cys Met Ser Ile Leu
```

```
<210> 185
<211> 98
<212> PRT
<213> Homo sapiens
<400> 185
Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
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<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<210> 187
<211> 70
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1



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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -13..-1

 <400> 188

 Met Leu Phe Ser Leu Ser Leu Leu Ser Asn Leu Asn Gln Ile Gly Ser -10

 -8 Fer His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe In Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Gln Pro Ser Ala Asn Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn Ile Ile Tyr Ile Tyr Ile His Asn Ile His Asn Thr Ile Tyr Ile

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<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 189
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
       -40
                           -35
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                       -20
                                          -15
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
                   - 5
Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
                           30
Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                       4.5
Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu
                   60
                                      65
Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile
 75 80 85
Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu
Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys
                           110
                                              115
Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro
                       125
                                          130
Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu
                   140
                                      145
Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr
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160

165

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<210> 190
<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                                    10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
                                25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                            40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                       55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
                   70
                                        75
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                85
                                    90
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
           100
                               105
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
                            120
                                                125
Thr Met Glu Leu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                       135
                                            140
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
                   150
                                        155
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
               165
                                   170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
           180
                                185
Asp Thr Val Lys Ile Gln Lys Lys
       195
```

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<210> 191
<211> 379
<212> PRT
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<213> Homo sapiens

<220>
<221> SIGNAL
<222> -37..-1

<400> 191

 Met
 Pro
 His
 Ser
 Leu
 His
 Pro
 Ser
 Ile
 Pro
 Cys
 Pro
 Arg
 Gly
 His

 Gly
 Ala
 Gln
 Leu
 Val
 Leu
 Leu
 Ser
 Ala
 Cys
 Leu
 Val
 Thr

 Leu
 Trp
 Gly
 Leu
 Gly
 Pro
 Pro
 Pro
 Glu
 His
 Thr
 Leu
 Arg
 Tyr
 Leu
 Val
 Cys
 Leu
 Val
 Cys
 Leu
 Val
 Cys
 Leu
 Arg
 Tyr
 Leu
 Val
 Cys
 Leu
 Arg
 Gly
 Val
 Cys
 Leu
 Arg
 Gly
 Val
 Cys
 Leu
 Arg
 Gly
 Val
 Cys
 Leu
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 Tyr
 Arg
 Gly
 Ser
 Leu
 Arg
 Gly
 Ser
 Arg
 Tyr
 Arg
 Gly
 Cys
 Leu
 Arg
 Arg
 Gly
 Cys
 Leu
 Arg
 Arg



60 Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln 80 85 Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile 100 Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala 115 Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln 130 135 Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly 145 150 Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val 160 165 170 Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys 180 Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr 195 Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr 210 215 Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser 220 225 230 Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala 240 245 Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu 260 Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp 275 Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu 290 295 Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro 305 310 Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met 320 325 Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser

<210> 192 <211> 112 <212> PRT

<213> Homo sapiens

<400> 192

 Met
 Pro
 Ser
 Glu
 Gly
 Arg
 Cys
 Trp
 Glu
 Thr
 Leu
 Lys
 Ala
 Leu
 Arg
 Ser

 Ser
 Asp
 Lys
 Gly
 Arg
 Leu
 Cys
 Tyr
 Tyr
 Arg
 Asp
 Trp
 Leu
 Arg
 Arg

```
<211> 43
<212> PRT
<213> Homo sapiens
<400> 193
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
           20
                                25
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
       35
<210> 194
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
                       -10
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                                    10
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
                                25
Pro Asn Phe
       35
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
           -15
                                -10
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
                                            10
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
                   20
                                        25
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
Val Thr Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
                            70
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
```

Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

90



```
115
                                    120
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
            130
                                135
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
                            150
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
                        165
                                            170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
                    180
                                        185
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val
                195
                                    200
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
                               215
Arg Thr Ala Trp
        225
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<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 Ala Gly Pro Leu Ala Val Ala Val Leu Tyr His Lys Met Asn Asn 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 90 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 Gly Ile Tyr Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 185 190 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly



310

Leu

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

<400> 197 Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His

1 5 10 15
Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys Lys 20 25 30

<210> 198
<211> 112
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1

Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser
35 40 45

Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His
50 55 60

<210> 199
<211> 54
<212> PRT
<213> Homo sapiens
<400> 199
Glu Tle Ala Gly Tyr (

Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr
1 5 10 15

<210> 200



Pro Arg Trp His Arg Leu Pro Pro Gln Ser Leu Gln His His Gln Tyr
20 25 30

Cys Gln Arg Arg Trp Pro Asp Arg Arg Cys Leu Gln Ser His Thr Gln
35 40 45

Ser Ser Gly His Leu Pro
50

<211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 200 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 5 1 Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp 50 . .55 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 80 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 115

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

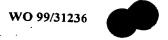
Gly Lys Val Lys Ser Phe Lys

PCT/IB98/02122

Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly 60 65 Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg 80 Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly 95 Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 105 110 115 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 145 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 155 160 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 175 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg Asn Ala Tyr Val 200

<210> 202 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<210> 203 <211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1



<210> 204 <211> 87 <212> PRT <213> Homo sapiens <400> 204

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 Glu
 Leu
 Ala
 Pro
 Thr
 Ala
 Arg
 Leu
 Pro
 Pro
 Gly
 His
 Gly
 Ser
 Leu

 Pro
 His
 Gly
 Val
 Leu
 Gly
 Pro
 Arg
 Ala
 Thr
 Gly
 Ser
 Val
 Thr
 His
 Leu
 Dro
 Glu
 Arg
 Ala
 Ser
 Glu
 Ala
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 Arg

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

10

<400> 206
Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

```
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Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser
                                                    30
                                25
Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro
Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr
                        55
Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu
                    70
                                        75
Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys
                                    90
Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val
                                105
           100
Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg
        115
                           120
His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys
                       135
Glu Glu Ala Ala Met Lys Ala Lys Thr Glu
                   150
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<210> 207 <211> 101 <212> PRT <213> Homo sapiens

TIP III

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -22..-1

100



			30					35					40		
Glu	Glu	Glu 45	Glu	Glu	Glu	Arg	Lys 50	Lys	Lys	Cys	Pro	Lys 55	Lys	Ala	Ser
	60	Ser				65					70	_	_		
75		Gln			80					85					90
		Lys		95					100					105	
		Lys	110					115					120		
Ala	Gln	His 125	Leu	Asp	-Asn-	-Va·l	Asp 130	Gln	Thr	Gly	Pro	Lys 135	Ala	Trp	Lys
Gly	Ser 140	Thr	Thr	Asn	Asp	Pro 145	Pro	Lys	Gln	Ser	Pro 150	Gly	Ser	Thr	Ser
Pro 155	Lys	Pro	Pro	His	Thr 160	Leu	Ser	Arg	Lys	Gln 165	Trp	Arg	Asn	Arg	Gln 170
Lys	Asn	Lys	Arg	Arg 175	Cys	Lys	Asn	Lys	Phe 180	Gln	Pro	Pro	Gln	Val 185	Pro
Asp	Gln	Ala	Pro 190	Ala	Glu	Ala	Pro	Thr 195	Glu	Lys	Thr	Glu	Val 200	Ser	Pro
Val	Pro	Arg 205	Thr	Asp	Ser	His	Gly 210	Ala	Arg	Ala	Gly	Ala 215	Leu	Arg	Ala
Arg	Met 220	Ala	Gln	Arg	Leu	Asp 225	Gly	Ala	Arg	Phe	Arg 230	Tyr	Leu	Asn	Glu
Gln 235	Leu	Tyr	Ser	Gly	Pro 240	Ser	Ser	Ala	Ala	Gln 245	Arg	Leu	Phe	Gln	Glu 250
Asp	Pro	Glu	Ala	Phe 255	Leu	Leu	Tyr	His	Arg 260	Gly	Phe	Gln	Ser	Gln 265	Val
Lys	Lys	Trp	Pro 270	Leu	Gln	Pro	Val	Asp 275	Arg	Ile	Ala	Arg	Asp 280	Leu	Arg
Gln	Arg	Pro 285	Ala	Ser	Leu	Val	Val 290	Ala	Asp	Phe	Gly	Cys 295	Gly	Asp	Cys
Arg	Leu 300	Ala	Ser	Ser	Ile	Arg 305	Asn	Pro	Val	His	Cys 310	Phe	Asp	Leu	Ala
Ser 315	Leu	Asp	Pro	Arg	Val 320	Thr	Val	Cys	Asp	Met 325	Ala	Gln	Val	Pro	Leu 330
Glu	Asp	Glu	Ser	Val 335	Asp	Val	Ala	Val	Phe 340	Cys	Leu	Ser	Leu	Met 345	Gly
Thr	Asn	Ile	Arg 350	Asp	Phe	Leu	Glu	Glu 355	Ala	Asn	Arg	Val	Leu 360	Lys	Pro
Gly	Gly	Leu 365	Leu	Lys	Val	Ala	Glu 370	Val	Ser	Ser	Arg	Phe 375	Glu	Asp	Val
Arg	Thr 380	Phe	Leu	Arg	Ala	Val 385	Thr	Lys	Leu	Gly	Phe 390	Lys	Ile	Val	Ser
Lys 395	Asp	Leu	Thr	Asn	Ser 400	His	Phe	Phe	Leu	Phe 405	Asp	Phe	Gln	Lys	Thr 410
Gly	Pro	Pro	Leu	Val 415	Gly	Pro	Lys	Ala	Gln 420		Ser	Gly	Leu	Gln 425	
3ln	Pro	Cys	Leu		Lys	Arg	Arg							. –	

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<211> 98

<212> PRT

<213 > Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1



<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1



50 Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr 65 70 Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn 100 95 Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr 115 110 Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile 130 Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu 145 Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe 160 Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val 180 175 Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys 190 195 Arg Lys Ser Arg Thr 205

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 100 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 Asn Asp Phe Ser Gln Glu Ser Ser 130

<210> 213 <211> 179 <212> PRT <213> Homo sapiens

-150- PCT/IB98/02122 ...

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<222> -54..-1
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                -50
                                    -45
Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala
            -35
Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Ala Ala Ala Ala
                            -15
Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys
Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro
                                    20
Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu
                                35
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Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
45 50 55

Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu
60 65 70

Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser 75 80 85 90 Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp

95 100 105
Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met

Asn Leu Ile 125

<210> 214

<211> 269 <212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -92..-1

<400> 214

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu
-90
-85
-80
Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro

Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro
-75 -70 -65

Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -60 -55 -50 -45

Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr
-40 -35 -30

Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala
-25 -20 -15

Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val

Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val
5 10 15 20

Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe

Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys
40 45 50

His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr 55 60 65

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Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn
                      75
Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala
                  90
Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln
               105
                                  110
Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu
           120
                              125
His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp
                          140
Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr
                                160
150 155
Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro
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<210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

110

-20

<400> 215 Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 100 Ser Ala Pro Lys Ser Asn Val

<210> 216 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -38..-1 <400> 216 Met Asn Asn Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser -35 -30 Val Lys Gly His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr

-15

Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu -5 1 5 5 10

Phe Asn Pro Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys 15 20 25

Glu Val Leu

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1

<400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Glu Ala -35 -30 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -20 -15 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50 Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr 65

<210> 218
<211> 376
<212> PRT
<213> Homo sapiens

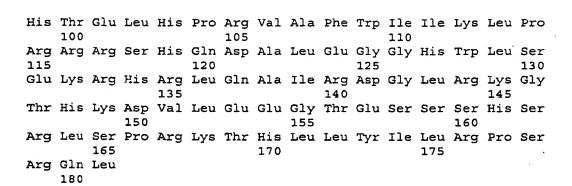
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<221> SIGNAL
<222> -21..-1

<400> 218
Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Leu Pro Pro



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100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
                            115
                                                120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                        130
                                            135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                                        150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
                                    165
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
                                180
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                            195
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
                        210
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
                    225
                                       230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
                240
                                   245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
            255
                               260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
        270
                           275
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                       290
                                            295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                                        310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
                                   325
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
                                340
Arg Ser Tyr Leu Pro Gln Ile Ser
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<210> 219
<211> 211
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 219
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                   -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
               ~10
                                    -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                            10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                        25
                                           30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
                   40
                                       45
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
               55
                                    60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met
                               75
Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe
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<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 220 Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 -30 • • Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -25 -20 -15 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu 25 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln

75

Pro Glu Phe His Ile Glu Ile Leu Ser Ile



Ala Val Ser Leu Ser Ala Pro Ala Phe Ala Ser Ala Leu Arg Ser Met Lys Ser Ser Gln Ala Ala Arg Lys Asp Phe Leu Arg Ser Leu Ser 15 Asp Gly Asp Ser Gly Thr Ser Glu His Ile Ser Ala Val Val Thr Ser 30 Pro Arg Ile Ser Cys His Gly Ala Ala Ile Pro Thr Ala Arg Ala Leu 45 Cys Leu Gly Cys Ser Cys Cys Thr Glu Arg Leu Leu Pro Pro Pro 60 Ser Leu Leu Ser Leu Glu Ala Pro Ala Ser Thr 75

<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 222

Met Ala Met Ala Gln Lys Leu Ser His Leu Leu Pro Ser Leu Arg Gln -15 Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr 40 Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu 55 Ala Ala Leu Val Leu Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val 70 Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu 85 Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln 100 Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val 115 120 125 Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr 130 135 Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro 145 150 Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn 165 Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val 175 180 185 Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg 200 Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr 210 215 His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Phe Phe Ser 225 230 Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly 240 245 250 Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

<210> 223

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PCT/IB98/02122 -
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270
                    275
                                        280
Glu Pro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu
                290
                                    295
Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu
                                310
Val Gln Arg Lys Leu Asp Gln Lys Thr Lys
        320
                            325
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<211> 210
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 223
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
                   -15
                                        -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
                            20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                        35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
                                85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                            100
                                                105
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                        115
                                            120
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                   130
                                       135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
               145
                                   150
His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu
           160
                               165
Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys
                           180
Pro Lys
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<210> 224
<211> 184
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
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190

<400> 224 Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser



-20 -15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 55 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150 His Leu Leu Ala Asp Thr Met Leu 160

<210> 225 <211> 227 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 225 Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -15 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 20 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 35 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp 65 Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80 85 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 95 100 Gln Gly Gln-Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 110 115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 130 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 160 165 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala

180

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PCT/IB98/02122
-158-
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Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile 190 195 Ala Ala Cys 205

<210> 226 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

<400> 226 Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu -35 -30 Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr -20 -15 Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile 15

Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu

70

<210> 227 <211> 73 <212> PRT <213> Homo sapiens

<400> 227 Met Glu Lys Tyr Glu Asn Leu Gly Leu Val Gly Glu Gly Ser Tyr Gly 10 Met Val Met Lys Cys Arg Asn Lys Asp Thr Gly Arg Ile Val Ala Ile 20 25 Lys Lys Phe Leu Glu Ser Asp Asp Lys Met Val Lys Lys Ile Ala 40 45 Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg His Glu Asn Leu Val 55 Asn Leu Leu Glu Val Cys Lys Lys

<210> 228 <211> 82 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 228

Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser -10 -5 Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp



Lys Asn

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<210> 229
<211> 119
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
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60

<210> 230 <211> 54

<400> 229 Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser -50 Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly -35 Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp -15 Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu 20 Ile Met Thr Ser Ser Phe Leu Ser Ser Glu Ile His Asn Thr Gly 30 35 Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro 50 Ile Leu Ala Lys Lys Lys

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<210> 231
<211> 210
<212> PRT
<213> Homo sapiens
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<220>

<400> 231

<221> SIGNAL <222> -14..-1

Met Leu Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val -10 - 5 Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr 10 Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu 25 Arg Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile 45 Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe 60 Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met 75 Thr Ala Tyr Leu Asp Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu 90 Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly 105 110 Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu 120 125 Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile 135 140 Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg 150 155 Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp 170 175 Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys

<210> 232 <211> 108 <212> PRT <213> Homo sapiens

<400> 232

Gln Glu 195

 Met
 Gly
 Cys
 Val
 Phe
 Gln
 Ser
 Thr
 Glu
 Asp
 Lys
 Cys
 Ile
 Phe
 Lys
 Ile
 Lys
 Ile
 Phe
 Lys
 Ile
 Ile</th

<210> 233 <211> 43



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<212> PRT
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 <222> -18..-1
 <400> 233
 Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu
            -15
                                 -10
 Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
   ______5____
 Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
 15
 <210> 234
 <211> 36
 <212> PRT
 <213> Homo sapiens
 <400> 234
 Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu
                                    10
 Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr
            20
 Phe Phe Gln Ile
        35
<210> 235
<211> 307
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -13..-1
<400> 235
Met Leu Ala Val Ser Leu Thr Val Pro Leu Gly Ala Met Met Leu
           -10
                                - 5
Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro
                        10
Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu
                    25
                                        30
Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile
                40
Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu
Glu Asn Gly Glu Ile Glu Thr Ile Ala-Arg Phe Gly-Ser Gly-Pro Cys
Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg
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105

Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu

Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser

Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr
135 140 145

110



Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 160 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Val 215 220 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 235 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala Lys Lys Lys

<210> 236 <211> 106 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1

<400> 236 Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu -30 -25 Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly -15 -10 Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met 10 Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn 40 45 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr Thr 70

<210> 237 <211> 42 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 237

Met Asp Leu Arg Gln Phe Leu Met Cys Leu Ser Leu Cys Thr Ala Phe -15 -10 -5 Ala Leu Ser Lys Pro Thr Glu Lys Lys Asp Arg Val His His Glu Pro



Gln Leu Ser Asp Lys Val His Asn Asp Ile 20

10

<210> 238 <211> 117 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -20..-1

<400> 238 Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser -15 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg 50 ... . 55 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70 Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile

85

95

Ile Asp Lys Thr Thr

<210> 239 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

<400> 239 Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe -30 Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile -15 Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe 15

Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu Ile Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val 35 Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn 55 Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 70 His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr 85 Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Pro Pro Ile Ile Phe

-10



75

90

Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys

```
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly 110 115 120

Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val 125 130

Ile Gly 140
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<210> 240
<211> 126
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
<400> 240
Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val
                            -20
Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser
Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile Phe Ile
                                    15
Ala Glu Val Ala Ala Val Val Ala Leu Val Tyr Thr Met Ala
Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr
                            45
Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly
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| Tyr | Tyr | Val | Leu | Phe | Lys | Leu | Leu | Arg | Asp | Asp

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                                        -15
                                                            -10
ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                       98
Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
                 -5
aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gcc
                                                                      146
Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                            15
cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                      193
His His Phe Ile His Pro Cys Leu Asp
                        30
aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
                                                                      253
agagggcagc acttatacct ggtggtcttt ctgatggtca gttttattcc cctcctgaat
                                                                      313
ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
                                                                      373
tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaag
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aggcaggcag tggagtctcc ctgtcgacag taaagttgaa atggtgacgt ccactgctgg
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ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
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tccatgcaca tttagttgcc tgcctgtggc tggtaaggta atgtcatgat tcatcctctc 613
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ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
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tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt
                                                                      793
tttaacactc tacatttccc ttgtttttta actcatgcac atgtgctctt tgtacagttt
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                                                   -15
ecc cet ctm wgc ege gee tte gee tge ege tgt caa etc get eeg
                                                                      100
Pro Pro Leu Xaa Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro
                        -5
gag cgc ggc gcc gag cgc agg gat aca gcg ccc agc ggg gtc tca aga
                                                                      148
Glu Arg Gly Ala Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg
                10
                                    15
ttc tgc cct cca aga aag tct tgc cat gat tgg ata gga ccc cca gat
                                                                      196
Phe Cys Pro Pro Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp
            25
                                30
aaa tat tca aac ctt cga cct gtt cac ttt tac ata cct gaa aat gaa
                                                                      244
Lys Tyr Ser Asn Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu
                            45
tct cca ttg gaa caa aag ctt aga aaa tta aga caa gaa aca caa gaa
                                                                      292
Ser Pro Leu Glu Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu
                        60
tgg aat caa cag ttc tgg gca aac cag aat ttg act ttt agt aag gaa
                                                                      340
Trp Asn Gln Gln Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu
                    75
                                        80
aaa gaa gaa ttt att cac tca aga cta aaa act aaa ggc ctg ggc ctg
                                                                      388
Lys Glu Glu Phe Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu
                90
aga act gaa tca ggt cag aaa gca aca ttg aat gca gaa gaa atg gcg
                                                                      436
Arg Thr Glu Ser Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala
            105
                                110
gac ttc tac aag gaa ttt tta agt aaa aat ttt cag aag cac atg tat
                                                                      484
Asp Phe Tyr Lys Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr
                            125
tat aac aga gat tgg tac aag cgc aat ttt gcc atc acc ttc ttc atg
                                                                      532
Tyr Asn Arg Asp Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met
                        140
gga aaa gtg gcc ctg gaa agg att tgg aac aag ctt aaa cag aaa caa
                                                                      580
Gly Lys Val Ala Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln
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aag aag agg agc aac taggagteea etetgaceea gecagagtee aggttteeae
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Lys Lys Arg Ser Asn
aggaagcara tggagctcct ttcacagggg ctctgagaaa aactggagct gatctcaaga
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15	20	aca gac cag gga att ggt Thr Asp Gln Gly Ile Gly 25	208
gga ttt gga gaa gag ccg Gly Phe Gly Glu Glu Pro 30	35	Kaa Xaa Met Xaa Leu Ile	256
cga tct gta aga acc gtg Arg Ser Val Arg Thr Val 45 att gca att gtg tta gt	50	Leu Ile Ile Val Asn Ser	304
att gca att gtg tta ctt Ile Ala Ile Val Leu Leu 60	65		354
atatettage toostast	caktaraa kttattac	tt tggtcattat tggaatattt	414
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						-	20					.ys 15	icu I	ieu i	rb Mra	
ctg	gca	atq	ata	acc	caa	cct	acc	tca	~~~	. ~~~		15			cca	
Leu	Ala	Met	Val	Thr	Ara	Dro	- מו	202	22	900	200	acg	990	ggc	Pro	101
-10			· • • •		-5	FIO	Ald	ser	AIA	. Ата	Pro	Met	GTA	Gly	Pro	
		~~~								1				5		
gaa Clu	Tau	yca	cag	cat	gag	gag	ctg	acc	ctg	ctc	ttc	cat	999	acc	ctg	149
GIU	ьeu	Ala	Gin	His	Glu	Glu	Leu	Thr	Leu	Leu	Phe	His	Gly	Thr	Leu	
			TO					15					20			
cag	ctg	ggc	cag	gcc	ctc	aac	ggt	gtg	tac	agg	acc	acq	gag	aaa	caa	197
Gln	Leu	Gly	Gln	Ala	Leu	Asn	Gly	Val	Tyr	Arg	Thr	Thr	Glu	Glv	Ara	
		25					30					35				
ctg	aca	aag	gcc	agg	aac	agc	cta	aat	ctc	tat	aac	cac	202	2+2	~~~	245
Leu	Thr	Lys	Āla	Arg	Asn	Ser	Leu	Glv	Leu	Tree	990	290	mb-	T)-	gaa ol	245
	40	_		_		45		1		+ y -	50 50	Arg	TIII	TIE	GIU	
ctc	cta	aaa	cag	gag	atc			~~~			50					
Lev	Len	Glv	GJD	Glu	77-1	es-	299	990	cgg	gat	gca	gcc	cag	gaa	ctt	293
55		O _T y	9111	Glu	CO	Set	Arg	GIA	Arg	Asp.	Ala	Ala	Gln	Glu	Leu	
-	~~~	~~~			60					65					70	
253	9Ca	age	ctg	ttg	gaa	act	car	atg	gag	gag	gat	att	ctg	cas	ctg	341
Arg	ALA	ser	ьeu	ьeu	Glu	Thr	Gln	Met	Glu	Glu	Asp	Ile	Leu	Xaa	Leu	
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cag	gca	rag	gcc	aca	gct	gag	gtg	ctg	9 99	gag	qtq	qcc	caq	qca	car	389
Gln	Ala	Xaa	Ala	Thr	Ala	Glu	Val	Leu	Gly	Glu	Val	Ala	Gln	Ala	Gln	202
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aag	gtg	cta	cgg	gac	agc	ata	cag	caa	cta	daa	ktc	C 2 C	ctc	2 2 2		437
Lýs	Val	Leu	Ara	Asp	Ser	Val	Gln	Ara	T.611	Yaa	Van	Cag	Tax	ary	asc	437
		105	_				110	5	LCu	naa	naa		теп	Aaa	лаа	
qcc	taa	cta	ggc	cct	acc	tac		333				115				
Ala	Tro	Len	G] V	Dro	777	Tur	N==	aaa	77-	gar	gtc	tta	aag	gcy	CCC	485
	120		O ± y	Pro	AIA	TAT	Arg	гÀг	Pne	Glu		Leu	Lys	Ala	Pro	
cck		222				125					130					
Dro	yam	aaı	car	aac	cac	atc	cta	tgg	gcc	ctc	aca	ggc	cac	gtg	cak	533
PIO	Aaa	гÀг	GIN	Asn	His	Ile	Leu	Trp	Ala	Leu	Thr	Gly	His	Val	Xaa	
133					140					145					150	
cgg	car	arg	cgg	gar	atg	gtg	gca	cag	cag	cwt	ckq	cta	cna	car	atc	581
Arg	Gln	Xaa	Arg	Glu	Met	Val	Ala	Gln	Gln	Xaa	Xaa	Leu	Xaa	Gln	Tle	501
				155					160					165		
cag	gar	aaa	ctc	cac	aca	aca	aca	ctc	cca	acc	toss	tete	+	~~~	ggaac	63.4
Gln	Glu	Lys	Leu	His	Thr	Ala	Ala	Leu	Pro	212	cgaa	receg	icc t	.ggat	ggaac	634
		-	170					175		ALG						
tgaq	gacc	aa r		ctac	2 20	assa	20++	-, -			-					_
qaqq	Lacc	ta t	tcac	tage	~ ay	3000	2000	- cca	cycc	eeg	cgag	gccc	ct g	rgca	gggag	694
agac	agac	-2 c	ccac	-229	a	agec	4999	cgc	caaa	CCC	cact	tctg	ag c	acag	agcar	754
-3~c	~3QC	ສບ	3909	yyga	c aa	aggc	agag	gat	gtag	CCC	catt	9999	ag g	ggtg	gagga	814
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<222> 886..897

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tgaggagetg gagetggtgg ggaetgggee gea atg gae aag etg aag gtg Met Asp Lys Leu Lys Lys Val												114				
									-5		ער ע	2 Te	u by	-		
ct	g ago	aaa	cao	gac	200	~~~	~~~	~~~						- 5	O	
Lε	g ago	GJA	Gln	Aen	Th~	Clu	yac nas	cgg	agc	agc	ctg	tco	gag	gtt	gtt	162
	u Ser		-45	Lap	1111	Giu	Asp	Arg	Ser	GIA	Leu	Ser	Glu	. Val	Val	
a=	ים מכם	tot						-40					-35			
G I	g gca	500	Coa	tta	agc	tgg	agt	acc	agg	ata	aaa	ggc	ttc	att	gcg	210
01	u Ala	OCL	261	Leu	ser	Trp	ser	Thr	Arg	Ile	Lys	Gly	Phe	Ile	Ala	
		-30					~25					-20				
25	t ttt	gct	ata	gga	att	ctc	tgc	tca	ctg	ctg	ggt	act	gtt	ctg	ctq	258
Cy		Ala	Ile	Gly	Ile	Leu	Cys	Ser	Leu	Leu	Gly	Thr	Val	Leu	Leu	
	10					- 10					-5					
tg	g gtg	ccc	agg	aag	gga	cta	cac	ctc	ttc	gca	ata	ttt	tat	acc	ttt	306
	p Val	Pro	Arg	Lys	Gly	Leu	His	Leu	Phe	Āla	Val	Phe	Tyr	Thr	Dhe	300
1				5					10				- / -	15	7116	
99	t aat	atc	gca	tca	att	aaa	agt	acc	atc	ttc	ctc	ata	~~ a		~+~	354
Gl	y Asn	Ile	Ala	Ser	Ile	Glv	Ser	Thr	Tle	Dhe	Ten	Mos	gga	D	gra	354
			20			1		25	+1C	FIIC	пец	Met		PFO	val	
aa	a cag	ctq	aaq	cga	ato	+++	aaa		205		<u>.</u>		30			
Ly	s Gln	Leu	Lvs	Ara	Met	Dhe	Glu	Dro	The	200	ttg	att	gca	act	atc	402
-		35	-1-			2110	40	PIO	THE	Arg	Leu	TTE	Ala	Thr	Ile	
at	a ata	cta	tta	tat	+++	~~	20					45				
Me	g gtg	Len	Leu	Car	Dha	31-	T	acc	ctg	tgt	tct	gcc	ttt	t g g	tgg	450
	t Val		пец	Cys	Pile	Ala	Leu	Thr	Leu	Cys	Ser	Ala	Phe	Trp	Trp	
cat		220	~~~			55					60					
Hi	t aac	Tree	994	CEE	gca	CLL	atc	ttc	tgc	att	ttg	cag	tct	ttg	gca	498
65	s Asn	гуя	GIY	ren	Ата	Leu	Ile	Phe	Cys	Ile	Leu	Gln	Ser	Leu	Ala	
					70					75					0.0	
7	g acg	Egg	tac	agc	ctt	tcc	ttc	ata	cca	ttt	gca	agg	gat	gct	ata	546
ьет	ı Thr	Trp	Tyr	Ser	Leu	Ser	Phe	Ile	Pro	Phe	Ala	Arg	Asp	Ala	Val	
				85					90					0=		
aaa	aad	tgt	ttt	gcc	gtg	tgt	ctt	gca	taat	tcat	aa c	cagt	ttta	+		593
To Y	naa	Cys	Pne	Ala	٧al	Cys	Leu .	Ala				5-		. •		333
-			10.0					105 -								
gaa	ıgcttt	gg a	aggc	acta	t aa	acag	aaac	taa	tara	cac	++++	atwa	ct a	+~++	66222	CE3
	Jegee	cc a	caya	catg	t gc	CEEE	tatc	tta	caac	aat (atat	tact	ta t	~>++	00000	653
		966	actt	LLGG	a aq	caac	aata	cat	tete	caa .	ccta	22+4	+	~+ ~ ~	~~~~	713
3	-3~3~u	9- 9	ggtt	CLUC	a cc	ttat	ggag	Laa	aatc	ttc :	ctca	+~+=	~~ +			773
ctg	gatgt	tg t	ccca	ctga	a tt	cccai	taaa	tac	2220	cts :	a	cyta aass		gitt	CCECE	833
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457

517 518

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                                                                      157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
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aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                      205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
                15
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                      253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
                                35
get act tge ecc ega gge tte gee gte acc gge tge act tgt gge tee
                                                                      301
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
        45
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
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Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro

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85

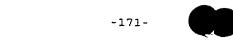
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Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu Phe Pro	
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Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp Leu Tyr	152
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Tie Pio Kaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser Gln Lys	
15 20 25	
ggg tot gcc atg gag ttg gca gtc atc acg gta rat ggc gta	
Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val	242
35 40	
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Judecedada dadaadad	350

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<222> 965..970

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-15 ttc ctg wgt cta atg acc ctg aca acc cat gtt cac tca agt gcc aag Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser Ala Lys -10 -5	164
CCa aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat Pro Asn Glu Gln Pro Trp Leu Leu Asn 5 10	211
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natgggtcca	cctgccggct	ggtccgaggg	cartataaat	cccakctctc	cgcaaccaaa	391
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gccaggtcag	tcaaatttgc	tagttcattt	gtcataaaca	taactcaaqt	tccaaatagg	931
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GIÀ	Arg	Leu -15	Cys	Leu	Leu	Thr	Ile	Val	Gly	Leu	Ile	Leu -5	Pro	Thr	Arg	104
GIA	Gln 1	Thr	Leu	Lys	Asp 5	Thr	Thr	tcc Ser	Ser	Ser 10	Ser	Ala	Asp	Ser	Thr 15	152
ııe	Met	Asp	Ile	Gln 20	Val	Pro	Thr	cga Arg	Ala 25	Pro	Asp	Ala	Val	Tyr 30	aca Thr	200
GIu	Leu	Gln	Pro 35	Thr	Ser	Pro	Thr	cca Pro 40	Thr	Trp	Pro	Ala	Asp 45	Glu	Thr	248
cca Pro	caa Gln	ccc Pro 50	cag Gln	acc Thr	cag Gln	acc Thr	cag Gln 55	caa Gln	ctg Leu	gaa Glu	gga Gly	acg Thr 60	gat Asp	GJA aaa	cct Pro	296
cta Leu	gtg Val 65	aca Thr	gat Asp	cca Pro	gag Glu	aca Thr 70	cac His	wak Xaa	agc Ser	mcc Xaa	aaa Lys 75	gca Ala	gct Ala	cat His	ccc Pro	344
act Thr 80	gat Asp	gac Asp	acc Thr	acg Thr	acg Thr 85	ctc Leu	tct Ser	gag Glu	aga Arg	cca Pro 90	tcc	cca Pro	agc Ser	aca Thr	kac Xaa 95	392



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atg acc Met Thr	cct tc Pro Se	100 t tct at r Ser Me	g atg a t Met A	ac aca Asn Thr	105 ccc t Pro S	cc gga er Glv	aac Asn	sgg Xaa	110 ggc	tgt	488
tgg tcg	cag ct	5 g tgc tg ı Cys Cy	t tca t	Ca cag	aca +	C2 + C2		125			536
gca agt	gca gg	agc to	ccc a	.35 rot tat	מככ מ	Ga ata	140				584
145	ALC GI	Ser Cy	150 G	Ty Tyr	Ala G	ly Ile	Ile	Ala	Gly	Glu	
160	Arg Asr	Arg Sei	. ;								632
5544546	aca gacy	accgtg (rggage	caq qqc	taccar	at ccca	atati	+	200+	~~~~	692 752
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<222> 583..593

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1	5	ı ren ren (Gin Ser Pro	ggc ttg aca Gly Leu Thr	Trp Ser	149							
	ccc act ggg Pro Thr Gly 20	g aga gaa g ' Arg Glu (gga aag gaa Gly Lys Glu 25	ggt ggg gat Gly Gly Asp	cgg gga Arg Gly	197							
35	naa Giy Aia	40	Ala Arg Ser	cct cag ggc Pro Gln Gly	Lys Glu	245							
atg ggg aga Met Gly Arg 50	caa agg acc Gln Arg Thr	aga aag o Arg Lys V 55	gtg aag ggc Val Lys Gly	cct gct tgg Pro Ala Trp	akt cac Xaa His	293							

aca gca aat cag gaa cta aac agg atg agg tot ctg tot tot ggc													PCT/II	398/0212:			
	Thr 65	Ala	Asn	Gln	Glu	Leu 70	Asn	Arg	Met	Arg	Ser 75	Leu	Ser	Ser	Gly	Ser 80	341
															aag Lys 95		389
															Gly ggg		437
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							att Ile			taaa	ataaa	act o	ctgaa	araco	et		580
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<221> polyA_site <222> 1104..1114

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	30					35					40					
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AIA	vaı	ser	Leu	Thr 65	Lys	Leu	Val	Arg	Gly 70	Arg	aaa Lys	Ala	Pro	Phe 75	Pro	501
vai	GIY	Asp	ser 80	GIÀ	Ser	Gly	Arg	Gly 85	Leu	Gln	cct Pro	Ser	Pro 90	gga Gly	tgt Cys	549
tat Tyr	cgc Arg	tat Tyr	tgaa	tata	tt g	tcct	gaco	a tg	aata	ggac	caa	cgtc	aat			598
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RUCC	acto	ct t	gatg	gcgc	t ga	cctt	cctc	wtg	tcct	cct	tcac	cttc	tg t	ggtk	ccttc	718
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acciii	+++	777	cgee	regg	s tr	csaa	tggc	tgg	gtgt	tcc	tgtt	ggct	ta t	gtta	gtccc	898
tata	====	+0 =	3010	acaa	a gc	aack	aaac	ccc	atgg	att	atcc	tgtt	ga g	gatg	ctttc	958
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gagcaa	g atg	Ctg Leu ~30	agc	aag	ggt	ctg	aag	cgg	aaa	cgg	gag	gag	gag Glu	gag		169
gag aa Glu Ly	g gaa s Glu -15	Pro	ctg Leu	gca Ala	gtc Val	gac Asp -10	tcc. Ser	_tgg. Trp	tgg. Trp	cta Leu	gat Asp -5	-cct	aac	cac His		217 -
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gac ct Asp Le	ı ser	Val	Leu 20	Lys	Leu	His	His	Ser 25	Leu	Gln	Xaa	Ser	Xaa 30	ccg Pro		313
gac ct	g cgg	cac	ctg	gtg	ctg	gtc	atr	aac	act	ctg	cgg	cgc	atc	cag		361



Asp	Leu	Arg	His 35	Leu	Val	Leu	Val	Xaa 40	Asn	Thr	Leu	Arg	Arg 45	Ile	Gln	
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Ala	Ser	Met 50	Ala	Pro	Ala	Ala	Ala 55	Leu	Pro	Pro	Val	Pro 60	Thr	Pro	Pro	
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Ala	Ala 65	Pro	Xaa	Val	Ala	Asp 70	Asn	Leu	Leu	Ala	Ser 75	Ser	Asp	Ala	Ala	
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Arg	Ser	Ile	Gly	Gly	Xaa	Pro	Pro	Xaa	Leu	Gly	Ala	Leu	Asp	Leu	Leu	
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			ctg													793
Ата	Pro	GIU	Leu		GIU	Ala	GIU	Leu		Tyr	Leu	Met	Asp		Leu	
~-~				180					185					190		
			cag													835
val	GIY	IIII	Gln 195	Ala	Leu	GIU	Arg	200	PIO	GIĀ	Pro	GIY	Arg 205			
taac	recet			7 <i>(</i> 7 = = †	-	-+~+	-+		+~		200			a+ ~~:	accaac	895
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Met	Glu	Thr	Leu	Tyr	Arg	Val	Pro	Phe	Leu	Val	Len	Glu	Cve	Dro	Asn	100
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Leu	Lys	Leu	Lys	Lys	Pro	Pro	Trp	Leu	His	Met	Pro	Ser	Ala	Met	Thr	134
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Pro	Lys	Leu	Asn	Arg	Phe	Leu	Leu	Leu	Phe	Ile	Gly	Phe	Val	Cvs	Val	- 12
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ueu .	naa	Ser	Phe	Xaa	Xaa	Ala	Arg	Val	Phe	Met	Arq	Met	Lvs	Leu	Pro	150
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	بعوع	ya c	gaca	LLLC	t ga	tttt	caga	aat	taac.	ata	aaat	ccaa	aa o	caad	attcc	905
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بودور	-grg	at g	gtag.	atta	t tt	cagai	tatg	tate	gtaa	aac	tatti	tact	ga a	caat	aagat	1025
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<210> 256 <211> 971

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<221> polyA_site <222> 961..971

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Gln Thr Asn Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr

-15 -10 -5

ctc tct gtc aca caa ccg tgg tac cta gaa gtg gac tac act cat gag 146

Leu Ser Wal Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu

_	
4	
•	

	1				5					10					2 5	
gcc	gto	: acc	: ata	aag	tgt	acc	tto	tcc	aca	acc	gga	tac	cct	+ -+	15 gag	3.04
NIG	. vaı	. Inr	ile	: Lys 20	Cys	Thr	Phe	Ser	Ala 25	Thr	Gly	' Cys	Pro	Ser	Glu	194
caa	cca	aca	tgc	ctg	tgg	ttt	cgc	tac	ggt	gct	cac	cag	cct	a a	aac	242
Gin	PIO	Inr	35	Leu	Trp	Phe	Arg	Tyr 40	Gly	Ala	His	Gln	Pro	Glu	Asn	
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	65	_Deu	_⊔у.ъ	-G1-U	ASN	70	vaı	Ser	Leu	Thr	Val 75	Asn	Arg	Val	Thr	-
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Lea	Val	130	пеп	Leu	ser	vaı	1yr 135	Vai	Thr	Gly	Val	Cys	Val	Ala	Phe	
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aga cag gtg tgg gga gag gtg cca gag ccc agt gat cgt tct gag gag



Arg Gln Val Trp Gly Glu	u Val Pro Glu Pro Ser 20	Asp Arg Ser Glu Glu 25
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	•	tat cta ata ttt Tyr Leu Ile Phe 60	_	
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Val Leu Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp
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Lys	Ile	Asn	Asp	Ala	Thr	Gln	Glu	Pro	Val	Asn	Cys	Thr	Asn	Tyr	Thr	
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Ala	His	Val	Ser	Cys	Phe	Pro	Ala	Pro	Asn	Ile	Thr	Cys	Lys	Asp	Ser	
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	_	65					70	•				75			-	
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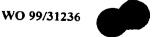
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Met	Leu	Ile	Met -10	Leu	Gly	Ile	Phe	Phe	Asn	Val	His	Ser	Ala 1	gtg Val	Leu	209
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aac Asn 20	ata Ile	tac Tyr	aac Asn	ctt Leu	tac Tyr 25	rag Xaa	caa Gln	ktc Xaa	agc Ser	tac Tyr 30	aac	tgt Cys	ttc Phe	atc Ile	gct Ala 35	305
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ctt c	ag gag ln Glu				ggc					tgt					496
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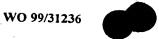
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aag	aaa	gtt	ctc	ctc	ctq	atc	aca	acc	atc	tta	aca	ata	act	~++	ggt	107
Бур	-15	val	Leu	Leu	Leu	11e	Thr	Ala	Ile	Leu	Ala	Val	Ala	Val	Gly	107
ttc	cca	gtc	tct	caa	gac	cak	gaa	cqa	gaa	aaa	aga	agt	atc	aat	gac	155
Phe	Pro	Val	Ser	Gln	Asp	Xaa	Glu	Ara	Glu	Live	Ara	Ser	TIO	Cor	Asp	155
_				5					10					15	_	
agc	gat	gaa	tta	gct	tca	999	ttt	ttt	gtq	ttc	cct	tac	cca	tat	CCa	203
Ser	Asp	Glu	Leu	Ala	Ser	Gly	Phe	Phe	Val	Phe	Pro	Tyr	Pro	Trer	Dro	203
			20			-		25				- 7 -	30	TYT	FIU	
ttt	cgc	cca	ctt	cca	cca	att	CCa		CC3	262			50			
Phe	Ara	Pro	T.eu	Dro	Dro	TIO	Dwa	Dha	D	aya		cca -	rgg	בבב	aga	251
		35			Pro		40					4.5				
cgt	aat	ttt	cct	att	cca	ata	cct	gaa	tct	acc	cct	aca	act	ccc	ctt	299
Arg	Asn	Phe	Pro	Ile	Pro	Ile	Pro	Glu	Ser	21=	Pro	The	The	77-0	Ton	233
	50					55					60				ьeu	
ccg	agc	gaa	aag	taaa	caag	aa c	qaaa	agto	a co	ataa	acct	aat	Cacc	·+~=		351
Pro	Ser	Glu	Lys			_				,		390	cacc	.cga		351
65			_													
aatt	gaaa	tt a	agee	actt	c ct	taar	·~==+								acaaa	
tata	atto	aa a	tage	2020	- ~	2541	gaal	- caa	aatt	CCT	gtta	атаа	aa g	jaaaa	acaaa	411
acat	Gaaa	~~ a	2222	2220	a gc	allo	ccta	gtc	aata	tct	ttag	tgat	ct t	cttt	aataa	471
	_ uaa	gc a	aaaa	aaaa	a aa											493

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<222> 96..182

<223> Von Heijne matrix
 score 5
 seg ELSLLPSSLWVLA/TS

<221> polyA_site

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totcatocag oggotgogga actgggogto ogggo atg acc tgo agg gga ago	113
Met Thr Cys Arg Gly Ser -25	
tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc ctc cca	161
Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	101
-20 -15 -10	
ago too otg tgg gto ota goo aca ago tot oca aca att act att goa	209
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala	
-5 1 5	
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tca tkt cgt Leu Ala Met Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	257
10 15 20 25	
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg	302
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	
30 35 40	
tagetgecae tgaaaaraag geggtgaete cageteetee cataaagagg tgggagetgt	362
cctcggacca gccttacctg tgacactgca ccctcacggc cacccgacta ctttgcctcc	422
ttggatttcc tccagggaga atgtgaccta atttatgaca aatacgtara gctcaggtat	482
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aaacaggctg ctggcattga ggtctgctac aaaaanarta atg gtc cca tgg ccc	175
Met Val Pro Trp Pro	
-55	
agg ggc aag gtg aaa act gct cct att ccc atc tct agg ttt cct ttc	223
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe -50 -45 -40	
ctc cct acc cac gac cca ccc acc cca gca cat tgg tct cca gca tct	271
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser	~ , _
-35 -30 -25 -20	
cat cag cag ttt aaa cat kkg tca ccc ctc ctc act ttg gcc ctg ctg	319
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	
-15 -10 -5	
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa	367
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	
1 5 10	
aaa gca aaa aaa tta cct tcc ttc tcc agc ctg ccc ctg aca ctc tgg	415



	15					20		Ser			25					
30	ьеи	Inr	Pro	Gin	Phe 35	Ala	Glu	ctc Leu	Thr	Thr 40	Val	Ala	Gln	Lys	Lys 45	463
neu	Arg	Trp	Ser	Gly 50	Thr	Leu	Gly	tgg Trp	Gly 55	Pro	Val	Pro	Ser	Trp	Val	511
GIII	Pne	Pne	ьеи 65	GIY				jaraç								566
tatg ktgg	gtca tggc ccca	ac c tc a	gctt	ggaa tgta	a at a ta	aktt	gaac	aca act	gtac	aat gar	aara acca	tatt aktt	tt g	aggo	ttagc tggga tcact aaaaa	626 686 746 806 811
211 212	> 29 > 62 > DNI > Hot	5 A.	apie	ns												

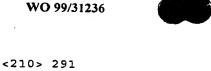
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<222> 594..599 <221> polyA_site <222> 613..625

<400> 290

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attategtga cageeteeta etgettetet ateatgtgge cagagetate tteeetaaaa	120
algeatigea tagitgatea agicaetete iggeetaaaa eetteetigg eteestasta	180
ccctcaggat aaagtetgga cccctcage atg get tgt gag act cat ggt gte Met Ala Cys Glu Thr His Gly Val	233
-30 -25	
ctt gtc cct gct cac ctc tct ggt ctc atc act tgc ctt ctt gca ttc	281
Leu Val Pro Ala His Leu Ser Gly Leu Ile Thr Cys Leu Leu Ala Phe -20 -15 -10	
tgg gtc cca gcc tcc tgt atc cag aga tgc agt ggc tct cca ttg cca	220
Trp Val Pro Ala Ser Cys Ile Gln Arg Cys Ser Gly Ser Pro Leu Pro	329
<u>-</u>	
Ctc tgattcctcc ttattcctcc	
Leu Leu	382
acceptance and a state of the s	4.40
accetggeat actacacara teactetggg eteacttgee tgeetaatgg teateteee	442
agtaaactgt aaggtgcttg aggasagg tttatttgcc tgcctaatgg tcatctcccc	502
agtaaactgt aagctccttg agggcaagga ttgtgttgga atttttgtat taacagtgcc	562
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<222> 650..655
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                                                                       120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                       180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                    Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                     -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                - 5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
                                                                      381
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
                        10
aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
getteectan ecetgaette ceaageetta gteateacee teteteecae ecagggetea
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gcacagtacc tggaacagtc aagccctcaa taaatgttta ctgagtgcat yaaaaaaaa
                                                                      681
aaa
                                                                      684
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<210> 292
<211> 628
<212> DNA
<213> Homo sapiens
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<221> CDS
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      seq KMLISVAMLGAXA/GV
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 <222> 618..627
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 ctgtgcaggc ggcc atg gat tcc ttg cgg aaa atg ctg atc tca gtc gca
                                                                      60
                                                                     110
                 Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala
 atg ctg ggc gca rgg gct ggc gtg ggc tac gcg ctc ctc gtt atc gtg
 Met Leu Gly Ala Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val
                                                                     158
 acc ccg gga gag cgg cgg aag cag gaa atg cta aag gag atg cca ctg
 Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu
                                                                    206
                 15
                                    20
 Gln Asp Pro Arg Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu
                                                                    254
             30
 ctg gec act ctg cag gag gca gcg acc acg cag gag aac gtg gcc tgg
                                                                    302
 Leu Ala Thr Leu Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp
                            50
 agg aag aac tgg atg gtt ggc ggc gaa ggc ggc gcc acg gga kgt cac
Arg Lys Asn Trp Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His
                                                                    350
    60
                        65
cgt gag acc gga ctt gcc tcc gtg ggc gcc gga cct tgg ctt ggg cgc
Arg Glu Thr Gly Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg
                                                                    398
                    80
                                       85
agg aat ccg agg cag ctt tct cct tcg tgg gcc can cgg aaa atc cgg
Arg Asn Pro Arg Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg
                                                                    446
                95
                                   100
ame gaa aat wee atg cca gga etc tee ggg gte etg tgaactgeeg
                                                                    492
Xaa Glu Asn Xaa Met Pro Gly Leu Ser Gly Val Leu
                               115
tegggtgage acgtgteece caaaccetgg actgactget ttaaggteeg caaggeggge
                                                                    552
cagggccgag acgcgagtcg gatgtggtga actgaaagaa ccaataaaat catgttcctc
                                                                    612
cammcaaaaa aaaaah
                                                                    628
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<223> Von Heijne matrix

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<222> 801..812

score 8

<221> sig_peptide <222> 50..244

490



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Ala	Pro	Leu -60	Ser	Cys	Leu	Ser	ccg Pro -55	Thr	Lys	Trp	Ser	Ser -50	Val	Ser	Ser	106
Ala	Asp -45	Ser	Thr	Glu	Lys	Ser	gcc Ala	Ser	Ala	Ala	Gly -35	Thr	Arg	Asn	Leu	154
cct Pro -30	ttt Phe	cag Gln	ttc Phe	tgt Cys	ctc Leu -25	cgg Arg	cag Gln	gct Ala	ttg Leu	agg Arg -20	atg Met	aag Lys	gct Ala	gcg Ala	ggc Gly -15	202
att Ile	ctg Leu	acc Thr	ctc Leu	att Ile -10	ggc Gly	tgc Cys	ctg Leu	gtc Val	aca Thr -5	ggc	gtc Val	gag Glu	tcc Ser	aaa Lys 1	atc Ile	250
tac Tyr	act Thr	cgt Arg 5	tgc Cys	aaa Lys	ctg Leu	gca Ala	aaa Lys 10	ata Ile	ttc Phe	tcg Ser	agg Arg	gct Ala 15	ggc Gly	ctg Leu	gac Asp	298
aat Asn	cyg Xaa 20	agg Arg	ggc	ttc Phe	agc Ser	ctt Leu 25	gga Gly	aac Asn	tgg Trp	atc Ile	tgc Cys 30	atg Met	gcg Ala	tat Tyr	tat Tyr	346
gag	agc	ggc	tac	aac	acc	aça	qcc	car	acq	atc	cta	gat	gac	aac	agc	394

Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu
70 75 80

rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt 538

Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val
85 90 95

aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt 586

Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys
100 105 110

60

45

Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser

atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc

Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg

gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg

40

55

gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc
Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser
115 120 125

taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc 691 caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg 751 gaaaattaag ctatacttt aagaaaataa atatttccat ttaaatgtca amaaaaaaaa 811 ah

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<212> DNA

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<221> CDS

<222> 154..576

<221> sig_peptide

<222> 154..360

<223> Von Heijne matrix score 4.80000019073486 seq MMVLSLGIILASA/SF

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<222> 737..742
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<221> polyA_site <222> 763..775

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ctggaaccaa d	egggcacagt	tggcaacacc	atc	atg	aca	tca	caa	cct	gtt	ccc Pro	1	.74

met im ser din pro val pro	
-65	
aat gag acc atc ata gtg ctc cca tca aat gtc atc aac ttc tcc caa	222
The lie val Leu Pro Ser Asn Val Ile Asn Dhe Cer Cla	
gca gag aaa ccc gaa ccc acc aac cag ggg aan aan	270
The block of the first Ash Gin Giv Gin Ash Cor Tour Tree Tree	270
Cat cta cac gca gaa atc ass gtt att ggg age	
His Leu His Ala Glu Ile Lys Val Ile Gly Thr Ile Gln Ile Leu Cys	318
ggc atg atg gta ttg agc ttg ggg atc att ttg gca tct gct tcc ttc	
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe	366
-10 -10 -10 -10 -10 -10 -10 -10 -10 -10	
tet cea aat tit ace caa gig act tet aca etg tig aac tet get tae	414
The Thi Gill val Thr Ser Thr Leu Leu Asn Ser Ala Tyr	
10	
Cca ttc ata gga ccc ttt ttt gtr akt aaa btt tct gag gag ggc agg	462
and the City Flo Phe Phe Val Xaa Lys Xaa Ser Glu Glu Gly Arg	
~~	
atg ggg caa ara ggg gag gaa rat vcc aat agc tta aac ttc cca sct	510
or near Gry Gru Gru Ada Xaa Ash Ser Len New Die Dee	510
**U	
got ago tig ota tki tig ato tgo cag gay gan and the	550
Ala Ser Leu Leu Xaa Leu Ile Cys Gln Xaa Gln Gly Phe Asn Gly Glu	558
55 60 6-	
tet tet tet eet gee geg targataaca gegetteett mettet	_
Ser Cys Ser Pro Val Gly	606
70	
caatttctta tcagactcaa ataaacattt cttttgaaaa tcatcttatt cttcacatta	
tcatcttgag ctatgatgga aactagtgas ktctctccag gtttaggcga aaaaaaaatc	666
catgaattag gataaagttg ggaaggaaga thittaggega aaaaaaaatc	726
catgaattag gataaagttg ggaaggaaca ttttatacaa aaaaaaaaah cc	778

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tac	aac	caa (caaa	caca	at to	acca	acac	c ato	a ato	a ac	uggo a toa	aget a caa	a coi	t at	t ccc	174
									Me	Th:	r Se	r Gli	n Pro	o Vai	l Pro	1/3
					gtg											222
		-60			Val		-55					-50				
ca	gag	aaa	CCC	gaa	CCC	acc	aac	cag	999	cag	gat	agc	ctg	aag	aaa	270
	-45				Pro	-40					-35					2.00
lis	Leu	His	\gca \ala	Glu	rtc Xaa	Lvs	Val	Tle	999	act Thr	atc	Cag	atc	ttg	tgt	318
30	200			OIU	-25	БуЗ	Vai	116	Gry	-20	116	GIII	116	neu	-15	
gc	atg	atg	gta	ttg	agc	ttg	999	atc	att	ttg	gca	tct	gct	tcc	ttc	366
				-10	Ser				-5					ı		
ct	cca	aat	ttt	acc	caa	gtg	act	tct	aca	ctg	ttg	aac	tct	gct	tac	414
		5			Gln		10					15			_	
ca	Dhe	ata	gga	CCC	ttt	ttt	ttt	atc	atc	tct	ggc	tct	cta	tca	atc	462
	20				Phe	25					30					
					tta Leu											510
5	4411	-	Буз	Arg	40	1111	N211	пец	beu	45	птэ	THI	IIII	Leu	50	
ga	agc	att	ctg	agt	gct	ctg	tct	gcc	ctg	gtg	ggt	ttc	att	ayc	ctg	558
				55	Ala				60		-			65		
ct	gtc	aaa	cag	gcc	acc	tta	aat	cct	gcc	tca	ctg	cak	tgt	gag	ttg	606
			70		Thr			75					80			
aa	Lvs	Asn	Agn	Tle	cca Pro	Thr	Yaa	Yaa	Tur	gtt	yct	Tac	Dho	Tat	cat	654
		85					90		-			95		-		
					acg											702
	100				Thr	105					110					
ga lv	Thr	T.AII	CCT	ctg	atg Met	ctg	att	tgc	act	ctg	ctg	gaa	ttc	tgc	cwa	750
-, 15		Dea	561	пец	120	пец	116	Cys	1111	125	Leu	GIU	PHE	Cys	130	
ct	gtg	ctc	act	gct	gtg	ctg	cgg	tgg	aaa		gct	tac	tct	gac		798
aa	Val	Leu	Thr	Ala 135	Val	Leu	Arg	Trp	Lys 140	Gln	Ala	Tyr	Ser	Asp 145	Phe	
ct	<u>aaa</u>	agt	gta	ctt	ttc	ctg	cct	cam	agt	tac	att	ggw	aat	tct	ggm	846
			150		Phe			155					160			
tg	tcc	tca	aaa	atg	acy	cat	gac	tgt	gga	tat	gaa	gaa	cta	ttg	act	894
		165			Thr		170			_		175			Thr	
~+	taac	aaaa	aaa c	aggac	gaaat	a tt	aato	agaa	act	toat	tct	tato	ratas	ıta .		947

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 <222> 433..444
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                                                                    120
 ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                                                                    172
                            Met Gln Val Pro His Leu Arg Val Trp
                                -35
 aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
                                                                    220
 Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
         -25
                            -20
 agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                    268
 Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                        -5
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
                                                                    322
 Lys Lys Arg Lys Leu Xaa Leu Phe
                10
tattgttgtt ttgctttttc tgccttcaaa ctactcccac aggccaaata tavctggctg
                                                                    382
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                                                                    442
aa
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score 7.5

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titing atg gtg gcc ctg aac ctc att ctg gtt ccc tgc tgc gct gct tgg	170
Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp	
-10 -5 1	210
tgt gac cca cgg agg atc cac tcc cag gat gac gtg ctc cgt agc tct Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser	218
5 10 15	
gct gct gat act ggg tct gcg atg cag cgg cgt gag gcc tgg gct ggt	266
Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly	
20 25 30	
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35 40 45	
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Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu	
55 60 65	
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Gly His Arg Ile Cys Asp Leu 70	
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aaaaatcaga acaaaacttc tattatccag agtcatggga gagtacaccc tttccaggaa	593
taatgiittg ggaaacactg aaatgaaatc ticccagtat tataaattgt qtatttaaaa	653
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Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro -55 -50 -45	
ate cca gtt cct cca agg ggc ctg ggt gct ggg gag ggg tca ggt agt	158
Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser	
-40 -35 -30	

cca gtg cgt cca cct gta tcc acc tgg ggc cct agc tgg gcc cag ctc Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu



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ctg	gac	agt	gtc	cta	tgg	ctg	999	gca	cta	gga	ctg	aca	ato	cag	gca	254	
тел	Asp	Ser	Val	Leu	Trp	Leu	Gly	Ala	Leu	Gly	Leu	Thr	Ile	Gln	Ala		
ato	-10 +++	+00	200			-5					1				5		
Val	ttt Phe	Ser	Thr	Thr	ggc	cca	gcc	ctg	ctg	ctg	ctt	ctg	gto	agc	ttc	302	
• • • •	Phe	Jei	7117	10	GIY	PIO	Ala	Leu		Leu	Leu	Leu	Val		Phe		
ctc	acc	ttt	gac		ctc	cat	add	ccc	15	~+-				20			
Leu	Thr	Phe	Asp	Leu	Leu	His	Ara	Pro	Mla	Val	aca Th~	CTC	tgc	cac	agc	350	
			25				3	30	A.a	val	1111	ьец	Cys 35	HIS	ser		
gca	aac	ttc	tca	cca	ggg	gcc	aga	gtc	agg	aaa	cca	ata	220	atc	cta	398	
 Ala	Asn	Phe	Ser	Pro	Gly	Ala	Arg	Val	Arg	Gly	Pro	Val	Lvs	Val	Leu		_
		40					45					50					
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Asp	Ser 55	Arg	Arg	Leu	Tyr	Ser	Суѕ	Lys	Trp	Val	Gln	Ser	Gln	Asp	Asn		
tts		+				60					65						
Len	gcc Ala	Ser	Ara	aag	cac	tgc	tgc	tgc	tgc	tca	tgg	ggc	tgg	gcc	cgc	494	
70	Ala		Arg	шуз	75	Cys	Cys	Сув	Cys		Trp	Gly	Trp	Ala			
	tgaa	aacc	ta t	gaca		·~ ++	- CMP C	cete		80	· -				85		
Ser	-		- _ _	55			. 		,	.ggcc	cgg	CEEE	ctg	cet		547	
ccat	tcctt	g g g	cctg	akan	c cc	ctcc	ccac	aac	tcac	tat	catt	caaa	ta t	- 2 - 2 =	tgacc	607	
acco	cttct	tc a	aaaa	aaaa	a aa					,050	0000	cuuu	.ca (Jacas	regace	629	
																027	
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\Z13	3 > Ho	mo s	apie	ns													
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			_		-	-		J	,			900	Met	Glu	Ara	57	
														- 7 5	_		
ctc o	gtc c	ta a	cc c	tg t	gc a	.cc c	tc c	eg c	tg g	ct q	tq a	ca t	ct d	act c	rac	105	
 Leu I	Val L	eu-1	nr - L	eu C	ys T	hr L	eu P	ro I	eu A	la V	al A	las	er 2	Ala C	ilv		-
		-	10				-	5				7					
tgc g	gcc a	cg a	.cg c	ca g	ict c	gc a	ac c	tg a	gc t	gc t	ac c	ag t	gc t	tc a	ag	153	
Cys ,	Ala T 5	nr T	nr P	ro A	ла А	rg A	sn L	eu S	er C	ys T	yr G	ln C	ys I	he I	ys	_	
•	•				1	0				1	5						
gtc a Val s	er c	gu t er m	yy a	eg g	ag t	gc c	cg c	CC a	cc t	gg t	gc a	gc c	cg c	tg g	ac	201	
Val S 20	5	-1 1	TP I	יוד ה	iu c	ys P	ro P	ro T	nr T	rp C	ys S	er P	ro I				
caa c	itc +	ac >	tc +			ac ~	t~ -	+	3 • - •	0				3	5		
	,	J- 4		a	uu y	ay y	LY G	LC a	cc t	CT fr	rr a	at a	an t	CV C	CC	240	

caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt agt gag tcy ccc Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser Glu Ser Pro



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cct Pro	ctc Leu	wkc Xaa 70	gac Asp	tta Leu	bct Xaa	atg Met	act Thr 75	cct Pro	cgg Arg	ckc Xaa	ycc Xaa	agg Arg 80	gcc Ala	tgg Trp	ggc Gly	34	5
cck Pro	gtg Val 85	ggt Gly	ccd Pro	aaa Lys	gtg Val	cct Pro 90	cct Pro	gct Ala	gtc Val	tct Ser	ccc Pro 95	gcg Ala	ctg Leu	ggc Gly	tcg Ser	39	3
ggc Gly 100	gag Glu	cat His	ccs Pro	rva Xaa	btg Xaa 105	tgaa	tkkk	ga o	tttt	ttct	c ck	ccat	ttga	a		44	1
agto	tcac	ta g	ggaac	tgto	a go	agga	caaa	ggc	tctg	gatg	tcac	tgaa	tt t	acaa	araca	a 50	1
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ggca	cago	ac a	artac	acct	g co	atac	aacc	car	cato	agg	cake	ctgo	ac t	ggaa	tcgat	62	1
acag	itgta	itg a	acaat	gtca	it at	agta	taac	aca	acat	aat	gaat	ataa	.cg t	gtat	attg	68	1
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atg aak ttc gaa tgg tcg ccg gcc ccc atg gtg caa ggc gtg atc acc Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly Val Ile Thr 70 75 80	345
agg cgc tgc tgt tcc tgg gct ctc tgc aac agg gca ctg acc cca cag Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln 85 90 95	393
gag ggg cgc tgg gcc ctg cra ggg ggg ctc ctg ctc cag gac cct tcg Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln Asp Pro Ser 100 115	441
agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys	489
ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln Glu Gly 135 140 145	534
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att ggg cta act ttg ctg cta gga rtt caa gcc as Ile Gly Leu Thr Leu Leu Leu Gly Xaa Gln Ala Me -10 -5 1	itg cct gca aat cgc 160											
ctc tct tgc tac aga aag ata cta aaa gat cac aa Leu Ser Cys Tyr Arg Lys Ile Leu Lys Asp His As 10	ac tgt cac aac ctt 208 sn Cys His Asn Leu											
CCG gaa gga gta gct gac ctg aca cag att gat gt Pro Glu Gly Val Ala Asp Leu Thr Gln Ile Asp Va 25 30	tc-aat-gtc-cag-gat256 al Asn Val Gln Asp 35											
cat ttc tgg gat ggg aag gga tgt gag atg atc tg His Phe Trp Asp Gly Lys Gly Cys Glu Met Ile Cy 40 45	ys Tyr Cys Asn Phe 50											
aag cga att gct ctg ctg ccc aaa aga cgt ttt ct Lys Arg Ile Ala Leu Leu Pro Lys Arg Arg Phe Le 55 60 65	eu Trp Thr Lys Asp 5											
ctc ttt cgt gat tcc ttg caa caa tca atg aga at	to tto atg tat tot 400											

418

478

538

598

612

P	CT/IB98/021
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Leu Phe Arg Asp Ser Leu Gln Gln Ser Met Arg Ile Phe Met Tyr Ser 70 75 80 85	
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tctagtttct atatagtgca atagagcata gattctataa attcttactt gtctaagaaa gtaaatctgt gttaaacaag tagtaataaa agttaattca atccaaaaaa aaaaaa	515 571
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aaa ctg ctt acc cac aat ctg ctg agc tcg cat gtg cgg ggg gtg ggg	106
Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val Gly -10 -5 1	
tcc cgt ggc ttc ccc ctg cgc ctc cag gcc acc gag gtc cgt atc tgc	154
Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile Cys 5 10 15	
cct gtg gaa ttc aac ccc aac ttc gtg gcg cgt atg ata cct aaa gtg	202
Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys Val 20 25 30	-
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag	250
Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln	
35 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagtttct	298
Val Pro Arg Arg Ala Gly 55	230

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ggaatctgga cgtatgttcc ccatcagccg cgggatcccc aacatgctgc tgagtgaaga

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Ser Thr	Gln Al	a Ser	act cca Thr Pro	Gly S	Ser Pro	Leu	Ser	Pro 15	Thr	Glu	Tyr	149	
Gln Arg 20	Phe Ph	e Ala	ctg ctg Leu Leu 25	Thr F	Pro Thr	Trp	Lys 30	Ala	Glu	Thr	Thr	197	
Cys Arg 35	Leu Ar	g Ala '	acc cac Thr His 40	Gly C	Cys Arg	Asn 45	Pro	Thr	Leu	Val	Gln 50	245	
Leu Asp	Gln Ty	r Glu 1 55	aac cac Asn His	Gly L	Leu Val 60	Pro	Asp	Gly	Ala	Val 65	Cys	293	
Ser Asn	Leu Pr 70	o Tyr I	gcc tcc Ala Ser	Trp P	Phe Glu 75	Ser	Phe	Cys	Gln 80	Phe	Thr	341	
cac tac His Tyr	Arg Cy 85	s Ser i	Asn His	Val T 90	Tyr Tyr	Ala	Lys	Arg 95	Val	Leu	Cys	389	
tcc cag Ser Gln 100	Pro Va	l Ser	Ile Leu 105	Ser P	Pro Asn	Thr	Leu 110	Lys	Glu	Ile	Glu	437	
sct tca Xaa Ser 115	Ala Gl	u Val 9	Ser Pro 120	Thr T	hr Asp	Asp 125	Leu	Pro	His	ctc Leu	acc Thr 130	485	
cca ctt Pro Leu	cac ag His Se	t gac a r Asp 1 135	aga acg Arg Thr	cca g Pro A	ac ctt sp Leu 140	cca Pro	gcc Ala	ctg Leu	gcc Ala			527	
tgagagg	ctc agc	acaac	g tggaag	gaget	cctaca	atcc	tcct	tgto	cc t	tggga	ggcca	587	
ggagcaa	gcg cca	gagcaca	a agcagg	gagca	aggagt	ggag	caca	ggca	igg a	agccg	acaca	647	
agaacac	aag cag	gaagag	g ggcaga	aaca	ggaaga	gcaa	gaag	agga	ac a	aggaa	gagga	707	
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gacagac	ata cas	naagte	o agteta	ectoc	tatest:	alct	ceca	accc	בכ ל	CCCC	ctcst	827 887	
tcgatca	gcc caq	aaata	g atgaaa	tgaa	tgaaata	atat	gato	acac	ict d	ctac	tggag	947	
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acg	Jacet	CTC	ctrg	rarm	icc c	cgac	tgag	g co	gaga	caaa	aat	acto	icad	acad	aacaaa	1	20
ago	ggca	aga	tcgc	atct	cc c	ggct	c at	9 99	c ga	c ta	t ct	g ct	g cg	c gg	t tac		73
						-	Me			рТу	r Le	u Le			y Tyr		
cac	ato	cta		a=a	- 200	+		-7					-7	0			
Ara	Met	Leu	Glv	Glu	Thr	Cyc	909	gac	tgc	999	acg	atc	ctc	ctc	caa	2:	21
		-65				Cys	-60	wah	Cys	GIY	Int	-55		Leu	Gln		
gac	aaa	cag	cgq	aaa	atc	tac			act	tat	cac		ctc	<i>~</i> 3 <i>~</i>	+	2	
Āsp	Lys	Gln	Arg	Lys	Ile	Tyr	Cvs	Val	Ala	Cvs	Gln	Glu	Leu	Aen	Ser	21	69
	-50		_	•		-45	-2-			0,0	-40			Asp	261		
gac	gtg	gat	aaa	gat	aat	ccc	gct	ctg	aat	qcc	cag	act	gcc	ctc	tcc	3.	17
Asp	var	Asp	Lys	Asp	Asn	Pro	Āla	Leu	Asn	Āla	Gln	Ala	Ala	Leu	Ser	٠.	. ,
-35					-30					-25					-20		
caa	gct	cgg	gag	cac	cag	ctg	gcc	tca	gcc	tca	gag	ctc	ccc	ctg	ggc	36	55
Gin	Ala	Arg	Glu	Hls	Gln	Leu	Ala	Ser	Ala	Ser	Glu	Leu	Pro	Leu	Gly		
				-15					-10					- 5			
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261	Arg	PIO	A1a	Pro	GIN	Pro	Pro	Val	Pro	Arg	Pro		His	Cys	Glu		
gga	act	aca	_	~~=	ata	224	5					10					
Glv	Ala	Ala	Ala	Glv	Len	Lve	yca Nla	712	cag	999	.cca	CCT	gct Ala	cct	gct	46	51
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gtg	cct	cca	aat	aca	rat		ato	acc	tac	303		202	gcc	c+ c	++~	-	
Val	Pro	Pro	Asn	Thr	Xaa	Val	Met	Ala	Cvs	Thr	Gln	Thr	Ala	Tien	Len	50)9
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Gln	Lys	Leu	Thr	Trp	Ala	Ser	Ala	Glu	Leu	Gly	Ser	Xaa	Thr	Ser	Xaa		,
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gga	aaa	mta	gca	tcc	agc	tgt	gtg	gcc	tta	tcc	gcg	cat	gtg	cgg	agg	60	5
GIY	ьys	Xaa	Ala	Ser	Ser	Cys	Val	Ala	Leu	Ser	Ala	His	Val	Arg	Arg		
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Pro	tgc	Mla	gcc	tgc	agc	agc	tac	agc	act	aag	aga	agc	CCC			64	7
	Cys	80 81a	wra	cys	∍er′	ser	1yr 85	ser	Thr	ьys	Arg		Pro				
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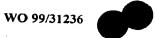
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	91
Met Ile Leu Cys Phe Leu Leu Pro His His -15 -10	
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Arg Leu Gln Glu Ala Arg Gln Ile Gln Val Leu Lys Met Leu Pro Arg	
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Glu Lys Leu Arg Arg Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys 15 20 25	
raa agg aca aaa tat gaa aca cca aga aaa rga raa gga aaa aaa gga 43	35
Xaa Arg Thr Lys Tyr Glu Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly 30 35 40	
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Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp	
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	Cys -5	Pro	Arg	Gln	Ala	Thr	Arg	Ile	Pro	Leu 5	Asn	Gly	Thr	Trp	Leu 10	Phe	•	
	acc	ccc	ata	age	aao	-	aca	act	ata	_	ant	a a a	++	2++		cgt	253	
	Thr	Pro	Val	Ser	Lvs	Met	Ala	Thr	Val	Lvs	Ser	Glu	T.e.	Tle	Glu	Arg	253	
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	пр	205	Leu	GIY	GIU	HIS		Asp	ser	Ser	Val		Val	Trp	Ser	Gly		
	ata		a+a	act	~~+	a+ a	210					215						
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	Thr	Asp	Lys	Asp	Pro	Glu	Gln	Tro	Lvs	Asn	Val	Hic	Lve	Glu	Val	Thr	925	
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	gca	act	gcc	tat	gag	att	att	aaa	atq		aat	tat	act			acc	973	
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	arg	Arg	Ile	His	Pro	Val	ser	Thr	Ile	Thr	Lys		Leu	Tyr	Gly	Ile		
	~=+	285	-		 _		290					295						
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	300	JIU	Glu	val	rne		ser	тте	PTO	Cys		Leu	Gly	Glu	Asn	_		
		acc	2	ct+	a + =	305	ata	~	a+ ~		310					315		
	Ile	Thr	æa.c Asn	Lev	Tle	Live	Tle	aay Lwe	Len	acc Th	Des	gaa	gaa	gag	gcc	cat	1165	
						y ==		⊸y 5	⊐∈ u	TIII	210	GIU	GIU	GIU.	ATA	nlS		

325



330

Leu Lys Lys Ser Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys 335 340 345	1213
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caggattata taacgaaatt ttgaataaac ttgaattcct aaaagatgga aacaggaaag taggtagagt gattttccta tttatttagt cctccagctc ttttattgag catccacgtg ctggacgata cttatttaca attcckaagt atttttggta cctctgatgt agcagcactt gccatgttat atatatgtag ttgrmatttg gttcccaaaa agtaggatgt aggtatttat tgtgttctag aaattccgac tcttttcatt agatatatgc tatttcttc attcttgctg gtttatacct atgttcattt atatgctgta aaaaagtagt agcttcttct acaatgtaaa aataaatgta catacaaaaa aaaaamcmc	1326 1386 1446 1506 1566 1626
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                                                                     120
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                                                                     180
 tggc atg gtg ctg acc acc ctc ccc ttg ccc tct gcc aac agc cct gtg
                                                                     229
      Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val
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 aac atg ccc acc act ggc ccc aac agc ctg agt tat gct agc tct gcc
                                                                     277
 Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala
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 ctg tcc ccc tgt ctg acc gct cca aag tcc ccc cga ctt gct atg atg
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 Leu Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met
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	gc cac er His 5														326
	ca gcg er Ala					tgat	caca	acg g	gaagg	gtgaa	ac a	cca	ggtc	B	377
gggat	gtgaa 1				caca										437
	acacc a ggcag d														497 557
	ggtat (617
tcwcgg	gtcwa d	gcca	acaga	at ca	agac	caara	a cca	aggc	ctct	gtc	cacc	stg 9	gccaa	acttgg	677
	atcat o														737
	atcta d aaagg a														797 857
	ccaa								_					-	917
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	ggag d														113
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ccc ac	a agg	caa	cat	cta	cta	atc	-30	cta	cta	ctc	ctc	-25 tct	200	cta	161
	la Arg														101
gtg at	c ccc	tcc	gct	gca	gct	cct	atc	cat	gat	gct	gac	gcc	caa	gag	209
Val II	le Pro	Ser	Ala	Ala		Pro	Ile	His		Ala	Asp	Ala	Gln		
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Ser Se	er Leu	Gly	Leu 15	Thr	Gly	Leu	Gln	Ser 20	Leu	Leu	Gln	Gly	Phe 25	Ser	23,
cga ct	t ttc	ctg		ggt	aac	ctg	ctt		ggc	ata	gac	agc		ttc	305



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Ser	Ala	Pro	Met	Āsp	Phe	Ara	ĞÎv	Leu	Pro	Glv	Asn	Tvr	Hie	LAZE	Glu		233
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gag	aac	cag	gag	cac	caq	cta		aac	aac	acc	ctc		200	Cac	ctc		401
Glu	Asn	Gln	Glu	His	Gln	Leu	Glv	Asn	Asn	Thr	Len	Ser	Ser	Uic	Leu		- U I
	60					65	2				70	JCI	561	1110	nea		
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		125		-			130					135	5		71.14		
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Glu	Gly	Gly	His	Trp	Leu	Xaa	Glu	Lys	Arg	His	Ara	Leu	Gln	Ala	Ile		•••
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Arg	Asp	Gly	Leu	Arg	Lys	Gly	Thr	His	Lys	Asp	Xaa	Leu	Xaa	Xaa	Glv		
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acc	gar	agc	tcc	tcc	cac	tcc	agg	ctg	tcc	ccc	cga	aar	amm	cac	tta		785
Thr	Glu	Ser	Ser	Ser	His	Ser	Arg	Leu	Ser	Pro	Arq	Lys	Xaa	His	Leu		
			190					195					200				
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Leu	Tyr	Ile	Leu	Xaa	Pro	Ser	Arg	Gln	Leu	_		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	_	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
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aar Lys	gca Ala -25	gct Ala	gjà aaa	cag Gln	atc Ile	cag Gln -20	gcc Ala	tgg Trp	tgg Trp	cgt Arg	999 Gly -15	gtc Val	ctg Leu	gtg Val	ege Arg	201
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ttr Leu	Gly 999	gtc Val 25	tac Tyr	gtc Val	atc Ile	cag Gln	gag Glu 30	cag Gln	gcg Ala	gcg Ala	gtc Val	aag Lys 35	ctc Leu	cag Gln	tcc Ser	345
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gag gtc cag aat cca gat gtt ctg tgg gat ttg gac atc ccc gaa gcc Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Ala -40 -35 -30	273
agg agc cat gct gac caa gac agc aac ccc aag gcg gaa gcc ctg ctc Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Leu Leu -25 -20 -15	321
ccc tgc aac ctg cac tgc agc tgg ctc cac agc agc ccc agg cca gat Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg Pro Asp -10 -5 1 5	369
ccc cat tcc cac ttc cca tct ktc agg agg tgc cct ttg ccc cac cct Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro His Pro 10 15 20	417
tgt gca acc tac ccc ccs kgc tgaaccactc tgtctcctat cctttggcca Cys Ala Thr Tyr Pro Pro Xaa 25	468
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803



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           Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn
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Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
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Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
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Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
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tgg gga ctc cgg cf Trp Gly Leu Arg Le -15				
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ctt tcc ttg gat ga Leu Ser Leu Asp G	lu Asn Glu Leu	gaa gag cag Glu Glu Gln 25	ttt gtg aaa gga Phe Val Lys Gly 30	cac 309 His
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WO 99/31236

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936

526





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200	722	a+ a	~~~		+ 0 >	~~~	+++	+ ~+	00+				-+-	-6		164
agc c																164
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Val V																
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Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser Leu Cys Phe Asn
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Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro Trp Cys Glu Ala
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His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr Asn Ser Asp Asn
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Pro	Leu	Leu	Leu	Glv	Arg	Ser	Ara	Lvs	Val	Ala	Ara	Glv	Ala	Pro	Val	
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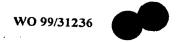


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cag tit tot tac cit tgc cig ccc tgc cit toa tgg aat aar aaa ggc	208
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ccc ctg cac ttt tct gat cta att tct gtt tta tac ctt ata ccc aaa Pro Leu His Phe Ser Asp Leu Ile Ser Val Leu Tyr Leu Ile Pro Lys -15 -10 -5	210
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Met Xaa Leu Val Leu Gly Lys Leu Leu Ser Gln 15 20	
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Cag cag cca ggt tcc ctc acc cca agc tca ccc act gtt ggg gag att Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu Ile -40 -35 -30	152
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Xaa	Gln	Gln	Pro	Asn 60	Gly	Ser	Leu	Ser	Leu 65	Asn	Ile	Ser	Ser	Ser 70	His	
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Ala	Pro	Xaa	Pro 75	Xaa	Thr	Cys	Thr	Leu 80	Glu	Pro	Gly	Val	Asp 85	Pro	Thr	
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Arg	Xaa	Val 90	Cys	Ile	Asn	Pro	His 95	Pro	Pro	Pro	Pro	Ile 100	Leu	Lys	Xaa	
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Pro	Leu 105	Ser	Pro	Tyr	Pro	Lys 110	Pro	Gln	Leu	Gly	Thr 115	His	Ala	Gly	Gln	
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Lys	Glu	Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	Gln	Ser	Ile	Val	Val	Ser		
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Tyr	Pro	Asp	Gln	Ile	Ile	Cys	Pro	Asp	Glu	Glu	Glv	Thr	Glu	Glv	Thr		
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Arg	Ala	Ala	Arg	Leu	Ser	Gly	Ala	Glu	Pro	Asp	Asp	Glu	Glu	Tyr	Gln		
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Glu	Phe	Glu	Glu	Met	Leu	Glu	His	Ala	Glu	Ser	Ala	Gln	Val	Ara	Thr		
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gtg	999	ata	gaa	aat	aga	aca	ctt	tac	ttc	ttc	cta	aaq	agg	cta			843
Val	Gly	Ile	Glu	Asn	Arg	Thr	Leu	Tyr	Phe	Phe	Leu	Lvs	Ara	Leu	Leu		
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	_	_	Gly								_					302
ביים	naa	25	Gly	пец	116	nc u	30	T Y T	n.a	1111	AIG	35	1111	rsp	116	
~~~	= a+		rct	ata	<b>+</b> a +	~~~		at a	222	at a	3. <b>c</b> +		3.4t	663	tas	410
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GIU	40	GIY	Xaa	Val	ıyı	45	Cys	Val	гуs	ьeu	50	Pile	261	PIO	Ser	
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	reu	Leu	Val	ASII		IIII	Asp	GIH	vaı	-	GIU	Tyr	ьys	Tyr	_	
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			agt													506
Arg	GIU	TTE	Ser		HIS	xaa	ıте	Asn		Hls	Xaa	GIY	Asn		TIE	
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Leu	Glu	Lys	Met	Thr	Phe	Asp	Pro		Ile	Phe	Phe	Asn		Leu	Leu	
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Pro	Pro		Ile	Phe	His	Ala	_	Tyr	Ser	Leu	Lys	-	Arg	His	Phe	
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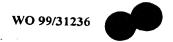
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ctc a	aaa	tac	ctc	cta	gat	222	aca	Cac	+ a+	<i>σ</i> +¬	a t a					264
Leu I	Lvs	CVS	Leu	Len	Acn	Lare	712	Uic	Cur	y.a	Tou	Leg	aca m-	Des	tgt 2	264
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aat t	- 2 -	a+c	+++		++~				20					25		
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Gly 1	тŸТ	116	30	ser	Leu	TTE	ser		GIu	Ile	Leu	Lys		Thr	Leu	
2 t a =		.						35					40			
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Lys										_						
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tataa	acai	tt c	aaca	ttad	a tt		++++	2++	+++-	222	cyya	gact	ta c	acaag	atata	821
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Met Arg
raa aag tgg aaa atg gga ggc atg aaa tac atc ttt tcg ttg ttc 165
Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu Leu Phe
-25 -20 -15 -10
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aca tat tgc atg ttt caa gac aag aag tac aga gtg ggt gag aga tgg
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Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp
                            15
cat cot tac ctg gaa cot tat ggg ttg gtt tac tgc gtg aac tgc atc
                                                                      309
His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile
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tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat
                                                                      357
Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn
                    45
                                        50
gtt cat tgc ctt tot cot gtg cat att cot cat ctg tgc tgc cot cgc
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Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys Pro Arg
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                                    65
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Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser
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Met

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Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val Gly

-15

-10

-5

gga gag acc agg atc atc aag ggg tte gag tge aag cet cae tee cag
Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln

1 5



ccc tgg cag gca gcc ctg ttc gag aag acg cgg cta ctc tgt ggg gcg	263
Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly Ala	•
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Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu Lys	
35 40 45	250
ccc cgc tac ata ktt cac ctg ggg cag cac aac ctc cag aag gag gag	359
Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu 50 55 60	
50 55 60 ggc tgt gag car acc cgg aca gcc act gag tec ttc ccc cac ccc ggc	407
Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro Gly	407
65 70 75	
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115 120 125	
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Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr Leu	
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Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn Ala	
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Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln Glu	
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Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys Ala	
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210 215 220	
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Trp Ile Gln Glu Thr Met Lys Asn Asn	000
225 230	
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cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	147
cgg ggc cta cta cac agt agc aaa tgg tcg gcg gag ttg gct ttc tct Arg Gly Leu Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser 25 30 35 40	195
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agg gcc att tta aaa tgt cat tct gcc ttt agt gaa aca tcc ata ttt Arg Ala Ile Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe 105 110 115 120	435
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	_		_site													
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								gga Gly							ttt	97
cct Pro	ggc Gly	tgt Cys 10	aga Arg	gcg	ctt Leu	tcc Ser	ccc Pro 15	tgg Trp	cgg	gtg Val	aga Arg	vtg Xaa 20	cag	aga Arg	cga Arg	145
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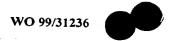
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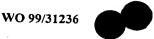


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242



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Pro Ser Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val
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                                -30
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Pro	GIA	Leu	His	Gln	ctc Leu	Thr	Lys	Leu 35	Xaa	Phe	Leu	Gln	Thr 40	Glu	Asp		350
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Asp 75	Pro	Asn	Glu	Cys	ggt Gly 80	Tyr	Gln	Pro	Pro	Gly 85	Ala	Pro	Pro	Gly	Leu 90		494
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xaa .	xaa	Thr	Arg 110	Ser	tgaa												597
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Ser Pro Leu Gly	/ Lys Val Ser Gln -30	Gly Pro Leu Phe Asn	Val Thr Ser
		-25	-20
Gly Ser Ser Ser	Dec Vel mbs mss	ttg ggc cta ctc tcc	ttc cag aac 265
	-15	Leu Gly Leu Leu Ser :	-5
ctg cat tgc ttc	cca gac ctc ccc	act gag atg cct cta	ara gcc aaa 313



Leu																
	His	Cys	Phe 1	Pro	Asp	Leu	Pro 5	Thr	Glu	Met	Pro	Leu 10	Xaa	Ala	Lys	
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tta		atc	tagg	tcca	aa c	ccca	akta	a ct	tact	даад	gaa	ctta	aaa	agta	gctgtt	425
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agti aati gta	ttcca tttat	aag g	caa	tct a	atg d Met I -50 cag	cat d His l	cat g His G	ggc (Gly) gtg	etc : Leu ! aaa	aca (Thr 1 -45 ttt	cca (Pro]	ctg Leu :	tta Leu aag	ctt (Leu (aaa	ggt Gly -40 aaa	
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80

85





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agt wet cat atg gga ttc cca raa aac ctg met aac ggt gcc act gct Ser Xaa His Met Gly Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala 110 115 120	590
gac aat ggt gat gat gga tta att ccm cca rgg aaa asc ara aca cct Asp Asn Gly Asp Asp Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro 125 130 135	638
gaa agc cas caa ttt cct gac act gag aat gaa cag tat cac agg gac Glu Ser Xaa Gln Phe Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp	686
140 145 150	
Phe Ser Gly His Pro Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln 155 160 165	731
tgatgaacaa aatgatactc hsaagcmmct ttctgaagam caraacactg gaatattaca	791
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,	•

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Glu	Leu	Xaa	Arg	Xaa	Asp	Arg	Xaa	Pro	Ser	Asn	Met	Xaa	Thr	Lys	Tyr		
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Ser	Thr	Val	Xaa	Thr	Thr	Leu	His	Ser	Met	Trp	Leu	Ser	Xaa	Pro	Leu		
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att	cac	agg	gtg	aag	cca	rat	ttg	gtg	ttg	tgt	aac	gga	cca	gga	aca	4.8	9
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tgt	gty	cct	atc	tgt	gta	tct	gcc	ctt	ctc	ctt	ggg	ata	cta	gga	ata	53	7
Cys	Val	Pro	Ile	Cys	Val		Ala	Leu	Leu	Leu	Gly	Ile	Leu	Gly	Ile		
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Lys	Lys	Val	Ile	Ile		Tyr	Val	Glu	Ser	Ile	Cys	Arg	Val	Lys	Thr		
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vai	GIn	\mathtt{Trp}	Pro	Ala	Leu	Lys	Glu	Lys	Tyr	Pro	Lys	Ser	Val	Tyr	Leu		
			185					190					195				
aāa -	cga	att	gtt	tgac	aaat	gg c	aact	gact	t ct	ttag	aatt	ttg	cast	taa		73	3
Gly	_	Ile	Val														
		200															
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-10



ggg ggc ttt gcc att gtg tat tac ctc att caa aag ttt cat tcc agg Gly Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg	218
act tta tat tac aag ttg gca gtg gar cag ctg car arc cat ccc gag Thr Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu	266
gca cag gaa gct ctg ggc cct cct ctc aac atc cat tat ctc aag ctc Ala Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu	314
atc gac agg gaa aac ttc gtg gac att gtt rat gcc aag ttg aaa att Ile Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile	362
cct gtc tct gga tcc aaa tca gag ggc ctt ctc tac gtc cac tca tcc Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser 65 70 75	410
aga ggt ggc ccc ttt cag agg tgg cac ctt gac gag gtc ttt tta gag Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu 80 85	458
ctc aag gat ggt cag cag att cct gtg ttc aag ctc agt ggg gaa aac Leu Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn 95	506
ggt gat gaa gtg aaa aag gag tagagacgac ccagaagacc cagcttgctt Gly Asp Glu Val Lys Lys Glu 110 115	557
ctagtccatc cttccctcat ctctaccata tggccactgg ggtggtggcc catctcagtg acagacactc ctgcaaccca gktttccagc caccagtggg atgatggtat gtgccagcac atggtaatt tggtgtaatt ctaacttggg cacaacgaat gctatttgtc atttttaaac tgaatccgaa agaaactcct attataaatt taagataatg taatgtattt gaaagtgctt tgtataaaaa agcacatgat aaaaggaatc agaattaata aaatgtttgt tgatctttaa aaaaaaaaaa	617 677 737 797 857 868
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ggc gtg agg acc atg caa gcc cga ggc ttc ggc tcg gat cag tcc gag	150

ggc gtg agg acc atg caa gcc cga ggc ttc ggc tcg gat cag tcc gag Gly Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu 1 5 10 15



aat gtc gac cgg ggc gcg ggc tcc atc cgg gaa gcc ggt ggg gcc ttc Asn Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe 20 25 30	206												
gga aag aga gag cag gct gaa gag gaa cga tat ttc cga gca cag agt Gly Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser 35 40 45	254												
aca gaa caa ctg gca rct ttg aaa aaa crc cat gaa gaa gar atc gtt Thr Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val 50 55 60	302												
cat cat aga gaa gga gat tgagcgtctg cagaaagaaa ttgagcgcca His His Arg Glu Gly Asp	350												
taagcagaag atcaaaatgc tagaacatga tgattaagtg cacaccgtgt gccatagaat 4 ggcacatgtc attgcccact tctgtgtaaa catggttctg gtttaactaa tatttgtctg tgtgctacta acagattata ataaattgtc atcagtgaaa aaaaaaaaa 5													
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-25 -20 cac acc ttc att gtc ctg cac ctg gtc ttg caa ggg atg gtt tat act His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr -15 -10 -5	159												
gag tac acc tgg gaa gta ttt ggc tac tgt cag gag ctg gag ttg tcc Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser 1 5 10 15	207												
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20 25 30													
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tcc aas cac tgc akt gtg tgt aac tgg tgt gtg cac cgt ttc rac cat Ser Xaa His Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His 85 90 95	447												





cac	tgt	gtt	tgg	gtg	aac	aac	tgc	atc	999	gcc	tgg	aac	atc	agg	tmc		495
His	Cys	Val	Trp	Val	Asn	Asn	Cys		Gly	Ala	Trp	Asn		Arg	Xaa		
++~	ctc	a+ c	100	~+~	++-			105		.			110				
Dhe	ctc	Tla	Tur	37.1	Tou	acc mh-	ttg	acg	gcc	tcg	gct	gcc	acc	gtc	gcc		543
F 11C	Leu	115	TYL	vaı	Leu	1111	120	ini	Ala	ser	Ala	125	Inr	vai	Ala		
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Ile	Val	Ser	Thr	Thr	Phe	Leu	Val	Hie	T.eu	Val	7723	Mot	Car) en	Lea		231
	130					135		*****	200	Val	140	Hec	SET.	Asp	пец		
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Tyr	Gln	Glu	Thr	Tyr	Ile	Asp	Asp	Leu	Gly	His	Leu	His	Val	Met	Asp		•••
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Thr	Val	Phe	Leu	Ile	Gln	Tyr	Leu	Phe	Leu	Thr	Phe	Pro	Arg	Ile	Val		
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Phe	Met	Leu	Gly	Phe	Val	Val	Val		Xaa	Phe	Leu	Leu	Gly	Gly	Tyr		
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Leu	Leu	Pne	Val	Leu	Tyr	Leu		Ala	Thr	Asn	Gln		Thr	Asn	Glu		
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225	Pro	PIO	ser	AIA	GIU	Pro	GIN	vai	Hls		Asn	Ile	His	Ser			
	a++				230					235					240		
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GIĀ	Leu	Arg	naa	245	neu	GIN	GIU	11e		Leu	Pro	Ala	Phe		Cys		
cat	~~~	200	226						250					255			
Hie	gag Glu	Arg	Luc	Tuc	Caa	gaa	tgac	magt	gt a	itgac	tgcc	t tt	gago	tgta	l		978
1110	014	AI 9	260	пуъ	GIII	GIU											
atte	ccgt	itt a		cace	+ ~+	aa+	ccto	. ~++	++~~				• •				220
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360

420

480

540

600

654



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		-40					-35					-30					
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Pro	Ser	Ser	Phe	Val	Ala	Ser	Cys	Pro	Thr	Leu	Leu	Pro	Phe	Ala	Cys		
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Val	Pro	Gly	Ala	Ser	Pro	Thr	Thr	Leu	Ala	Phe	Pro	Pro	Val	Xaa	Leu		
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	_		10		_	_		15					20				
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	40		- 2		_	45					50			-			
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		•															102
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Xaa Gly Arg Ala Arg Trp Leu Met Pro Val Ile Pro Ala Leu Gln Glu

-15

gcc gan gca ggc gga tca cga ggt cag gag ttt gaa act agc ctg gcc

750

Met Leu Xaa Leu Ser Arg Ala Thr Lys

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Ala Xaa	Ala Gly	Gly Ser	Arg Gly	Gln Glu		Thr Ser Lei 10	Ala				
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PCT/IB98/02122
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         Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg
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                                                                      159
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Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu
gca cac tot ttg toa ctg aga gac gtc tca gag agg ctg tgc agc tgc
                                                                      207
Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys
                            25
                                                                      255
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Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn
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ago tot gga gtg cac aga aaa toa ago agg ota tto tac ato ogg aca
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Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr
                                        60
                    55
cca atg aga aga tct tca tgc cat tta raa tgt cag gtt ata ttc ctt
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Pro Met Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu
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                                    75
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                                                                      406
Leu Gly Arg Gln Leu
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                                                                      466
tgcraccaag cetteacetg catecaagtt catecaggga tacetgggag etgteateag
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egeogtetee attgetgtgg geettatkte etggtteaga aageeaacaa gtteaeceea
                                                                      586
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631



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<221> polyA_signal



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	cag gga aga cgg ctg gga Gln Gly Arg Arg Leu Gly 20	
	cac cct gac gat gaa gcc His Pro Asp Asp Glu Ala 35	
	gcc cgc cta agg cac tgg Ala Arg Leu Arg His Trp 50 55	
	tac tac aat caa gga gag Tyr Tyr Asn Gln Gly Glu 70	
	gat gtt ttg ggg att cca Asp Val Leu Gly Ile Pro 85	ctc tcc agt gta atg 339
att att gac aac agg	gat ttc cca rat gac cca Asp Phe Pro Xaa Asp Pro	ggc atg cag tgg gac 387
	ara gtc ctc ctt cag cac Xaa Val Leu Leu Gln His 115	ata gaa gtg aat ggc 435
	act ttc gat gca ggg gga Thr Phe Asp Ala Gly Gly 130 135	rta agt ggc cac agc 483 Xaa Ser Gly His Ser
	tat gca gct gtg agg aag Tyr Ala Ala Val Arg Lys	ctt gag ggc caa att 531
tgc aag ccc tgt ggc	act gga caa gac ttt aag Thr Gly Gln Asp Phe Lys 165	gaa tgagtgctgt 577
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seq AMWLLCVALAVLA/WG

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gcg Ala	gtc Val	ttg Leu	gca Ala	tgg Trp 1	ggc	ttc Phe	ctc Leu	tgg Trp 5	gtt Val	-10 tgg Trp	gac Asp	tcc Ser	tca Ser 10	gaa Glu	-5 cga Arg	99
Met	Lys	Ser 15	cgg (Arg	Glu	Gln	Gly	Xaa 20	Arg	Leu	Gly	Ala	Glu 25	Ser	Arg	Thr	147
Leu	Leu 30	Val	ata Ile	Ala	His	Pro 35	Asp	Asp	Glu	Ala	Met 40	Phe	Phe	Ala	Pro	195
Thr 45	Val	Leu	Gly	Leu	Ala 50	Arg	Leu	Arg	His	Trp 55	Val	Tyr	Leu	Leu	Cys 60	243
Pne	ser	Ala	gtt Val	Phe 65	Arg	Arg	Glu	Leu	Ser 70	Glu	Tyr	Thr	Glu	Xaa 75	Leu	291
acc Thr	tct Ser	gaa Glu	CCC Pro 80	ctc Leu	ama Xaa	gcc Ala	tagg	gaca	igg a	rcgg	geegg	jc tt	acct	ggtg	Ī	342
ttgo	nstt	gg t	itgta	ttca	ıg ta	cctk	catt	tcc	gttg	gga	acto	cacc	wg t	actt	aacag gttat	402 462
kctg	ıtgga	ac t	tttt	ttta	it tt	gtag	aagg	ago	aaga	ata	ttga	cctt	ac t	atat	agcac	522
acga	aaca	at c	ctatg	ctgt	a to	gtgc	ctgc	tca	atcc	tta	aagt	taac	tt c	taat	gatag	582
taaa	arac	ct t	cctg	ctgo	c tt	taaa	atgo	ago	ttgt	gct	akta	acat	gc a	tgta	tcaaa	642
ttga	araa	itt a	agaca	taga	t ga	ctar	atar	aaa	gtaa	ttt	tgta	ggta	āt t	ttar	agttc	702
aact	ccac	cc a	igctt	tcak	t ga	agga	acct	ttc	aaat	aat	arat	tttt	gc t	tacc	atara	762
raaa	arat	ca a	atga	caaa	g ca	aata	ttga	cca	ttaa	gct	ggaa	tatg	gt g	ataa	ttqaa	822
cagt	tgta	ıta a	ıatga	akta	a tt	gaat	tgta	cac	atac	aat	gggt	gaat	tt t	atgg	catgt	882
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_			Val													
		_	-55		_	_		-50	•			_	-45			
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	_	_	Lys									-				
		-40	-	-	-		-35		_			-30			-	
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Asn	Thr	Lys	Gly	Asn	Thr	Leu	Lys	Glu	Glu	Trp	Ile	Ala	Tyr	Ile	Cys	
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Xaa	Glu	Ile	Leu	Arg	Gly	Leu	Xaa	His	Leu	His	Gln	His	Lys	Val	Ile	
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His	Arg	Xaa	Ile	Lys	Gly	Gln	Asn	Val	Leu	Leu	Thr	Glu	Asn	Ala	Glu	
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Val	Ile	Ala	Cys	Asp	Glu	Asn	Pro	Xaa	Ala	Thr	Tyr	Asp	Phe	Lys	Xaa	
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Asp	Leu	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Ile	Glu	Met	Ala	Glu	Gly	Leu	
		105					110					115				
ccc	ctc	tct	gtg	aca	tgc	acc	cca	tgag	gagct	ct d	ttcc	ctcat	cc co	ccgg	gaatc	642
Pro	Leu	Ser	Val	Thr	Cys	Thr	Pro									
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Arg Pro Arg Phe Val Ser Leu Arg Ala Lys Gln Asn Met Ile Arg Arg 10 15 20													
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ttc gag gcc ata aag gcg gcc gcc act tcc aag ttc ccc ccg cat aga Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser Lys Phe Pro Pro His Arg 60 65 70	296												
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_			cat	_		_	_	_	_				tga	aagg	cca		195
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-			_	_				_			-	_	-	aara	-	_	315
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ctca	ıggaç	igc t	gagg	gcago	ga ga	atc	gctta	aac	ctcgg	gag	gtag	gaggt	tg (cagt	gagc	ca	855
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wta kta tta ggc agg gca tac tcc tac cca ctc aac agt tat gaa ctc

289

495



Xaa Xaa Leu Gly Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu 45 50 55	209
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Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile	
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Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His	
-40 -35 -30	
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Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala	
-25 -20 -15 -10	
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Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val	
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-5 1 5	255
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65

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80

60

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		gac														591
His	Ser	Asp	Asn	Pro	Ser	Gln	Leu	Ile	Trp	Thr	Ser	Ser	Arg	Ser	Ala	
	105					110					115					
		tct														639
Arg	Lys	Ser	Asn	Phe	Ser	Leu	Glu	Asp	Phe	Gln	His	Ser	Lys.	Gly	Lys	
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Glu	Pro	Tyr	Ser	Ser	Ser	Lys	Tyr	Ala	Thr	Asp	Leu	Leu	Ser	Val	Ala	
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Leu	Asn	Arg	Asn	Phe	Asn	Gln	Gln	Gly	Leu	Tyr	Ser	Asn	Val	Ala	Cys	
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Pro	Gly	Thr	Ala	Leu	Thr	Asn	Leu	Thr	Tyr	Gly	Ile	Leu	Pro	Pro	Phe	
		170					175		_	•		180				
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Ile	Trp	Thr	Leu	Leu	Met	Pro	Ala	Ile	Leu	Leu	Leu	Arg	Phe	Phe	Ala	
	185					190					195	_				
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Asn	Ala	Phe	Thr	Leu	Thr	Pro	Tyr	Asn	Gly	Thr	Glu	Ala	Leu	Val	Trp	
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ctt	ttc	cac	caa	aag	cct	gaa	tct	ctc	aat	cct	ctq	atc	aaa	tat	cta	927
Leu	Phe	His	Gln	Lys	Pro	Glu	Ser	Leu	Asn	Pro	Leu	Ile	Lvs	Tvr	Leu	
				220					225				-	230		
agt	gcc	acc	act	ggc	ttt	gga	aga	aat	tac	att	atq	acc	caq	aaq	atq	975
Ser	Ala	Thr	Thr	Gly	Phe	Gly	Arg	Asn	Tyr	Ile	Met	Thr	Gln	Lvs	Met	
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		Asp														
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		Lys														
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															agcta	1242
ctca	igaac	iga t	gage	itaar	ia oc	atict	cttc	י פמר	ictac	idec.	2225	, out	, - u -	racto	gageta	1302
agat	tate	ים בני	ctar	acto	י~ שנ	cete	aato	, aca	ייים:	1027	SC#5	1+c+c	י בבי	y.t	gtata	1362
															ccttc	1422
															aaact	1422
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<221> CDS

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score 4.90000009536743 seq VLCTNQVLITARA/VP

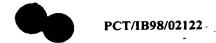
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tcactccaga tacatggaaa gatggtgcta ggaataccac agaaagtggt ggaagaaagc	180
tgaatgaaaa taaagetttg actteaaaaa aageeagaat tgateeata atg gaa gaa	238
Met Glu Glu	
-25	
ata agt tot coa ott gta gaa ttt gta aaa gtt ttg tgc acc aac cag	286
Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys Thr Asn Gln	
-20 -15 -10 gtt etc att act gee agg get gtg eet aca aaa aag gea tet gtg ega	334
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg	334
-5 1 5	
tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg	382
Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu	
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tot aga tgt att gat gga att tot ggo ttt ota aat gat ttt act tto	430
Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe	
30 35 40	
tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt	479
Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu	
45 50	
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aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttatttaa	599 659
cattattcat ataattctcc ccccaccact ttatttat	719
agataataaa tactttgctc tgaatttggc atccaaagtt aacatttctc ccctcactcc	779
cttgctggtg tcatagttat tagaatcagc agcctcttaa ctaattgcgg tttcatagga	839
tatataaatg tttcaagcca ttattgctga atggttcttt agttattaac ctagacccaa	899
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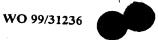
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-40

-35

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Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val



		-30					-25					-20						
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Æ	A1a	Gly	Ile	Leu	Phe	Phe	Thr	Gly	Trp	Trp	Ile	Met	Ile	Āsp	Āla	Ala		_
•	-15					-10					-5					1		
9	gtg	gtg	tat	cct	aag	cca	gaa	cag	ttg	aac	cat	gcc	ttt	cac	aca	tgt		254
'	/al	Val	Tyr	Pro	Lys	Pro	Glu	Gln		Asn	His	Ala	Phe	His	Thr	Cys		
_				5					10					15				
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	тУ	vaı	20	Ser	Inr	Leu	ATA	Pne	Phe	Met	Ile	Asn		Val	Ser	Asn		
_	ct	cad		202	aat	ast.	200	25	~				30					
2	la	Gln	Val	aga	Glv	yar Aen	age	Tur	gaa	agc	ggc	tgt	tta	gga	aga	aca		350
•		35		Arg	-Gry-	-yob	40	_1- y -1-	-GIU	ser	GIA		Leu	GIY	Arg	Thr		
c	at		cga	gtt	taa	ctt		att	aat	++~	2+~	45	2+~					200
ē	ilv	Ala	Ara	Val	Trn	Leu	Phe	Tle	G) v	Dhe	Mot	Ley	Mot	Dho	999	Com		398
5	้อ					55			-	- 110	60	Deu	Mec	PHE	GIY	65		
C	tt	att	gct	tac	atg	tgg	att	ctt	ttt	aat		tat	att	acc	caa	aat		446
I	eu	Ile	Ala	Ser	Met	Trp	Ile	Leu	Phe	Glv	Ala	Tvr	Val	Thr	Gln	Asn		440
					70	- ,				75		-1-			80			
a	ct	gat	gtt	tat	ccg	gga	cta	gct	gtg	ttt	ttt	caa	aat	qca	ctt	ata		494
T	hr	Asp	Val	Tyr	Pro	Gly	Leu	Ala	Val	Phe	Phe	Gln	Asn	Āla	Leu	Ile		
				85					90					95				
t	tt	ttt	agc	act	ctg	atc	tac	aaa	ttt	gga	aga	acc	gaa	gag	cta	tgg		542
P	he	Phe	Ser	Thr	Leu	Ile	Tyr	Lys	Phe	Gly	Arg	Thr	Glu	Glu	Leu	Trp		
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T	hr	Lgag	atca	act t	ctta	agto	a ca	tttt	cctt	ttg	ittat	att	ctgt	ttgt	ag			595
a	tag	gttt	tt t	atct	ctca	ıg ta	caca	ttgc	caa	atgo	agt	agat	tgta	ca t	taaa	tgtt	2	655
L	gtt	CCCC	tac	attt	ttat	g tt	ctga	gttt	tga	aata	att	ttat	gaaa	tt t	cttt	attti	-	715
C	cat	rgca	ta c	gactg	ttaa	ıt at	gtat	ataa	tac	aaga	cta	tatq	aatt	qq a	taat	gagta	a	775
C	cag	LLLL	TT 2	ittcc	tgag	a tt	taga	actt	gat	ctac	tcc	ctga	qcca	aa a	ttac	atcat	-	835
C.	ctg	tcat	tt t	agaa	gtaa	c ca	ctct	tgtc	tct	ctgg	ctg	ggca	caat	aa c	tcat	accto	7	895
E (aat	ccca	gc a	CTT	ggga	g gc	cgag	gcgg	gcc	gatt	gct	tgag	gtca	ag t	gttt	gagad	3	955
+4	29C	ctgg	cc a	acat	ggcg	a aa	CCCC	atct	act	aaaa	ata	caaa	aatt	ag c	cagg	catgo	, 1	015
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			cga Arg													197
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			gga Gly													293
ctg Leu	gaa Glu 60	agg Arg	gtg Val	aaa Lys	aga Arg	aga Arg 65	tgc Cys	cta Leu	gag Glu	aat Asn	ggc Gly 70	aat Asn	tta Leu	aaa Lys	gaa Glu	341
aaa Lys 75	gat Asp	ata Ile	ctt Leu	gtt Val	ttg Leu 80	ccc Pro	ctt Leu	gac Asp	ctg Leu	acc Thr 85	gac Asp	act Thr	ggt Gly	tcc Ser	cat His 90	389
			tac Tyr									tag	aatc	gac		435
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947



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Ala -5	Leu	Thr	Phe	Gly	Cys 1	Phe	Ile	Xaa	Thr 5	Ala	Phe	Lys	gac Asp	Arg 10	Ser	153
Val	Pro	Val	Arg 15	Leu	His	Val	Ser	Arg 20	Ile	Met	Leu	Lys	aat Asn 25	Val	Glu	201
Asp	Phe	Thr 30	Gly	Pro	Arg	Glu	Arg 35	Ser	Asp	Leu	Gly	Phe 40	atc Ile	Thr	Phe	249
gat Asp	ata Ile 45	act Thr	gct Ala	gat Asp	cta Leu	gag Glu 50	aat Asn	ata Ile	ttt Phe	gat Asp	tgg Trp 55	aat Asn	gtt Val	aag Lys	cag Gln	297
ttg Leu 60	ttt Phe	ctt Leu	tat Tyr	tta Leu	tca Ser 65	gca Ala	gaa Glu	tat Tyr	tca Ser	aca Thr 70	aaa Lys	aat Asn	aat Asn	gct Ala	ctg Leu 75	345
aac Asn	caa Gln	ktt Xaa	gtc Val	cta Leu 80	tgg Trp	gac Asp	aag Lys	att Ile	gtt Val 85	ttg Leu	aga Arg	ggt Gly	gat Asp	aat Asn 90	ccg Pro	393
													ttt Phe 105			441
Gly	Asn	Gly 110	Leu	Xaa	Gly	Asn	Arg 115	Asn	Val	Thr	Leu	Thr 120	ctg Leu	Ser	Trp	489
aac Asn	gtc Val 125	gta Val	cca Pro	aat Asn	gct Ala	gga Gly 130	att Ile	cta Leu	cct Pro	ctt Leu	gtg Val 135	aca Thr	gga Gly	tca Ser	gga Gly	537
cac His 140	gta Val	tct Ser	gtc Val	cca Pro	ttt Phe 145	cca Pro	gat Asp	aca Thr	tat Tyr	gaa Glu 150	ata Ile	acg Thr	aag Lys	agt Ser	tat Tyr 155	585
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        -5

        Ala
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        Ala
        Phe
        Leu
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        Ala
        Lys
        Val
        Asn
        Pro
        Phe
        Glu
        Xaa

        Phe
        Leu
        Ser
        Arg
        Gly
        Phe
        Trp
        Leu
        Cys
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Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg Phe Cys Pro Pro
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Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
               30
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
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Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
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Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
                       80
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
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Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
               110
                                    115
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
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                               130
Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met Gly Lys Val Ala
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Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln Lys Lys Arg Ser
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Asn
170
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Phe Gly

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Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala 15 20

Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg 35

Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu 50

Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 65 70

Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr 85

Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100

Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro 115

Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 130 135

His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu 145 150

Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His 160 165

Thr Ala Ala Leu Pro Ala 175

<210> 382

<211> 160

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 382

Met Asp Lys Leu Lys Lys Val Leu Ser Gly Gln Asp Thr Glu Asp Arg

<210> 383

-55 -50 -45 Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr -35 -30 -25 Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser -20 -15 Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr 20 Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro 30 35 Thr-Arg Leu Ile-Ala-Thr Ile-Met Val Leu Leu-Cys Phe Ala Leu-Thr 50 Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe 65 Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile 80 Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala 95 100

<211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 383 Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu Gly Leu Leu Val -15 Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly 20 Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro 40 Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser 55 Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met

70

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro

<210> 384 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 384 Met Ile Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu

-15 Phe Pro Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp

- 340



Leu Tyr Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser 15 20 Gln Lys Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val 35

<210> 385 <211> 27 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 385

Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser -15 -10 Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn

<210> 386 <211> 186 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -21..-1

<400> 386 Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp 20 Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly 50 Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys 65 70 Ala Ala His Pro Thr Asp Asp Thr Thr Leu Ser Glu Arg Pro Ser 85 80 Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu 100 Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly 115 Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser 130 Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile 145 Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser

-15



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<210> 387
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 387
Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu
  -15
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
                    -5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
                           30
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                                       65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                   80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                               95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                       125
                                          130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
135
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                   -50
                                       -45
```

 Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
 -50
 -45
 -40

 Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
 -35
 -25

 Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
 -25

 Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
 -10

 Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
 -5

 Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
 25

 Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
 30

 Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
 50

 Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
 60



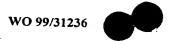
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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser 75 80 85
Pro Gly Cys Tyr Arg Tyr 90 95
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<210> 389
<211> 236
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 389
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
                       -25
                                           -20
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
                   -10
                                   -5
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Leu Phe Asp Leu
                              10
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                           25
Arq His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                       40
Met Ala Pro Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                                       60
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
               70
                                   75
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
                               90
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
                           105
                                               110
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
                       120
                                           125
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
                                       140
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
               150
                                   155
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                               170
           165
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
                          185
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
    195
                       200
```

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<210> 390
<211> 149
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -100..-1

<400> 390
Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
-100 -95 -90 -85
```



Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr -80 -75 Val Tyr Ala Leu Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile -65 -60 -55 Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp -50 -45 -40 Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn -30 Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met -15 Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile 1 _____5_ Pro Lys Leu Asn Arg Phe Leu Leu Phe Ile Gly Phe Val Cys Val 20

Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro 30 35 40 Gly Tyr Leu Met Gly

Gly Tyr Leu Met Gly

<210> 391

<211> 69

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -49..-1

<400> 391

 Met
 Pro
 Phe
 His
 Phe
 Pro
 Phe
 Leu
 Gly
 Phe
 Val
 Cys
 Leu
 His
 Leu
 His
 Leu
 Pro
 Phe
 Leu
 Pro
 Leu
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Pro
 Leu
 Pro
 P

Phe Phe Ile Pro Asp

20

<210> 392

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 392

والمنطابيين والمسواف بالمراطفية فللموادر والمناور والمناور والموادر والموادي والمناور والمالي والموادي المراط والمالوا و

205



200

Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 95 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 115 120 125 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln 170 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

Pro

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

10

30

35

Ser

<210> 395 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 395

<210> 396

<222> -24..-1

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro -20 -15 Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 15 20 Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 30 Trp Gly Gln Gly Thr His Ser Ser Leu 45

<211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 396 Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr -15 -10 Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu 5 Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu

35

20 Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala

<210> 397 <211> 192 <212> PRT

<220> <221> SIGNAL <222> -93..-1

<400> 397 Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn -90 -85 Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val



-70 -65 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -55 -50 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -40 -35 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn -25 -20 Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -5 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 25 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 45 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn 60 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys 75 Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln

<210> 398 <211> 149 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe -65 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 -45 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -35 -30 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 15 20 Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 30 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 45 50 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 60 Phe Ser Met Val Gly

<210> 399 <211> 73 <212> PRT <213> Homo sapiens

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
                   -15
                                       -10
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
                                5
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                            20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                       35
                                           40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                   50
                                       55 .
```

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<210> 401
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
```

Pro Xaa Lys Leu Arg Gln

<210> 400 <211> 86



45

50

55

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<210> 402
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 402
Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser
                         -20
           -25
Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
       -10
                            - 5
Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro
                   10
Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg
                                   30
               25
Thr
<210> 403
<211> 211
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
<400> 403
Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr
                           -20
Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe
                       -5
Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly
                                    15
Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn
                                30
Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His
                            45
Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro
                        60
Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser
                    75
                                        80
Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser
Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu
                                110
                                                    115
Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys
```

125

140

155

170

Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln

Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe

Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr

130

145

160

Arg Ser Ile

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<210> 404
<211> 123
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -80..-1
<400> 404
Met Ser Thr Trp Tv
```

Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp -75 -70 Ser Val Arg lle Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -60 -55 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -40 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -25 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -10 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 10 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 25 Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu

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<210> 405
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 405
Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile
                      -20
                                        -15
Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro
                  -5
Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu
                             15
Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu
                         30
Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His
Ala His Trp Xaa Ser Xaa
```

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<210> 406
<211> 162
<212> PRT
<213> Homo sapiens
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<220>
<221> SIGNAL
 <222> -31..-1
<400> 406
Met Ala Ala Trp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                    -25
                                    -20
Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
                    -10
Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
                            25
Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
                        40
Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
                70
Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                                90
Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
        100
                            105
                                                110
Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
 115
Pro Asn
130
<210> 407
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 407
Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile
                            -30
                                                -25
Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe
                        -15
Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu
```

Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln

Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu. Tyr Leu Leu Gly

Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met

<210> 408 <211> 70 <212> PRT

Val Arg 60

15

<213> Homo sapiens



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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
-15
                    -10
                               -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                           25
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
                       40
Asp Phe Ser Ser Phe Thr
50
<210> 409
<211> 60
<212> PRT
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<213> Homo sapiens <220> <221> SIGNAL <222> -45..-1 <400> 409 Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser -45 -40 -35 Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly -25 -20 Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser -10 - 5 Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys 5 10

<210> 411 <211> 51 <212> PRT

<210> 410 <211> 39



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<213> Homo sapiens
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<221> SIGNAL <222> -23..-1

<400> 411

Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala -20 -15 -10

Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
-5 1 5

Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg 10 20 25

Ile Trp Pro

<210> 412

<211> 95

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -48..-1

<400> 412

Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr
-45 -40 -35

Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn
-30 -25 -20

Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser -15 -10 -5

Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys Cys 1 5 10 15

Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu 20 25 30

Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val 35 40 45

<210> 413

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -32..-1

<400> 413

Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly
-30
-25
-20

Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys
-15 -5

Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser 1 10 15

Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser



```
<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
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<400> 414

<210> 415 <211> 190

Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro -75 -70 Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly -55 Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe -40 Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln -25 -20 Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe -10 -5 Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa 10 Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe 25 Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa 40 Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala 55 60 Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln 70 His Tyr Ile Arg His Ala Arg Gly Gly Leu

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
<400> 415
Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe
                            -75
His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly
                        -60
Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile
                                        -40
Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln
                                    -25
Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr
                                -10
Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile
Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile
                20
                                       25
Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu
               35
```



Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala Leu 50 55 60

Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 65 70 75

Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg His 80 85 90

Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu 95

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 416 Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -55 -50 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -40 -35 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -25 -20 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 30 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser Ser Lys

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -108..-1

<400> 417

 Met
 Thr
 Ser
 Gly
 Gln
 Ala
 Arg
 Ala
 Ser
 Xaa
 Gln
 Ser
 Pro
 Gln
 Ala
 Leu
 Leu
 -95
 Leu
 Thr
 Leu</th

<210> 418



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<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 418
Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                        -15
                                            -10
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
                                20
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
      30
                            35
Leu Arg Met
  45
```

<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1

100

<400> 419 Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -25 -20 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -10 -5 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu 20 25 Val Ala Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe 55 Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 70 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser



Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 115 120 125 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 135 140 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 165 170 . 175 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 180 185 190 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 195 200 205 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Glu Val Ile Gly Val Leu Trp 225 230 235 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 245 250 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 260 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 295

<210> 420 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 420 Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His -15 -10 Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His 10 His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn 20 25 Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val 30 35

Gly



-10 -5 1
Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
5 10 15
Glu Glu Gln Lys Xaa Ser Gly Ile Met
20 25

<210> 422
<211> 85
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -17..-1

<210> 423
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 423
Met Lys Lys Val Leu

65

<210> 424 <211> 69 <212> PRT <213> Homo sapiens



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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
            -25
                                   -20
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
           -10
                                -5
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                       10
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                    25
                                       30
Gln Xaa Ala Leu Leu
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
                        -50
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
                                        -30
                   -35
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
                                    -15
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
            -5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
                       15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
25
                    30
                                        35
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
                                    50
                45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
            60
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
```

Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly

Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln

-20

-5

-25

-10

<400> 426

Arg Cys Ser Gly Ser Pro Leu Pro Leu

<210> 427 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1

<210> 428
<211> 136
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 428
Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala

-15

Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu 10 Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg 20 25 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Ala Thr Leu 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 55 Met Val Gly Gly Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 100 Met Pro Gly Leu Ser Gly Val Leu

-10

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>



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<221> SIGNAL <222> -65..-1
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<400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 -55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -30 -25 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 85 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 100 105 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120

<210> 430 <211> 141 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -69..-1

<400> 430

Val Ser

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -30 -25 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 15 20 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 35 Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly

```
<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
```

<400> 431

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile -35 🦠 -30 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile 20 Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu 35 Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala 50 Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro 70 Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa 85 Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr 100 Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys 115 Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp 130 135 Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa 145 150 Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys 160 Gly Tyr Glu Glu Leu Leu Thr Ser 175

Phe

```
<210> 433
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
```

<400> 433

 Met
 Val
 Ala
 Leu
 Asn
 Leu
 Ile
 Leu
 Val
 Pro
 Cys
 Cys
 Ala
 Ala
 Trp
 Cys
 Cys
 Ala
 Ala
 Arp
 Cys
 Cys
 Cys
 Cys
 Cys
 Cys
 Ala
 Ala
 Trp
 Cys
 Cys
 Cys
 Cys
 Cys
 Cys
 Cys
 Cys
 Ala
 Ala
 Cys
 Ala
 Cys
 Ala
 Cys
 Ala
 A

<210> 435 <211> 121 <210> 436



```
<212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -16..-1
 <400> 435
 Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                         -10
 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
                                 25
 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
                             40
 Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                         55
 Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                     70
Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
 Leu Gly Ser Gly Glu His Pro Xaa Xaa
             100
```

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<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 436
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                        -10
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
           20
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys
                           40
Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                        55
Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
                    70
Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
                85
Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln
100 105 110
100-----
Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                           120
Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
Glu Gly
145
```

```
<210> 437
 <211> 110
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -20..-1
 <400> 437
 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
                     -15
                                          -10
 Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
                             20
 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                         35
 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
                     50
Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                 65
                                     70
 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
                                85
 <210> 438
<211> 71
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -15..-1
 <400> 438
Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                     -10
                                         -5
Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                                 10
                                                     15
Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                            25
Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
Gln Val Pro Arg Arg Ala Gly
50
<210> 439
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
```

Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys

-15

-20



```
      Ser
      Leu
      Asn
      Leu
      Leu
      Leu
      Gly
      Val
      Asn
      Lys
      Ile
      Ala
      Glu
      Lys

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Asp
      Pro
      Cys
      Lys
      Leu
      Asp
      Met
      Asn
      Phe
      Gly

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Lys
      Leu
      Asp
      Met
      Asn
      Phe
      Gly

      Ser
      Cys
      Tyr
      Phe
      Tyr
      Phe
      Tyr
      Asn
      Asn
      Arg
      Thr
      Ser
      Lys
      Asn
      Asn
      Leu
      Asn
      A
```

```
<210> 440
  <211> 169
  <212> PRT
  <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -25..-1
 <400> 440
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
                     -20
                                          -15
 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
                 - 5
 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                         30
 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                                         50
 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
                                     65
 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
                                 80
 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
                             95
 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
                         110
 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
                     125
                                                             135
 Arg Thr Pro Asp Leu Pro Ala Leu Ala
                 140
```

```
<210> 441
<211> 167
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -76..-1
<400> 441
Met Gly Asp Tyr Leu Leu Arg Gly Tyr Arg Met Leu Gly Glu Thr Cys
-75
-70
```

-322-



Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -40 -35 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -20 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 10 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 25 3.0 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -15..-1

Tyr Ser Thr Lys Arg Ser Pro

75

Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu 20 25 30 Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa Xaa

Xaa Leu Ser Lys Arg Asp

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL



```
Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
                                    25
  Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
                                  40
  Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
                             55
  Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                          70
  Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                      85
  Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
                 100
                                     105
  Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
                                 120
  Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
                             135
  Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                         150
                                             155
  Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                     165
                                         170
. Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
                 180
                                     185
 Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
             195
                                 200
 Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
         210
                             215
                                                 220
 Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
                         230
                                             235
 Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                                         250
 Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
                 260
                                     265
 Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
             275
                                 280
 Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                             295
 Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                        310
 Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
                    325
 Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
                 340
```

```
<210> 444
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14...-1
```



```
<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
    -35
                     -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                        -15
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                    1
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                        -20
                                            -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                   -5
                                        7
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
           10
                                15
Thr Arg Gly
       25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                    -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
                                    -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                            10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
```

Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly



```
35
                    40
                                        45
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
                55
                                    60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn
                                75
Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln
                            90
Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu
                       105
                                            110
Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His
                    120
                                        125
Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg
               135
                                    140
Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu
                               155
Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr
                           170
His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg
                       185
                                           190
Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg
                   200
                                       205
Gln Leu
```

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
Met Gly Ser Lys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
                   -55
                                      -50
Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys
               -40
                                   -35
Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
           -25
                               -20
                                                  -15
Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
        -10
                           - 5
Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln
Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu
                                  30
Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
                               45
Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe
                           60
Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln
75
Pro Glu Phe His Ile Glu Ile Leu Ser Ile
                   90
```

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

<210> 448 <211> 154

-35



```
<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
                                -50
                  -55
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                  -40
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
              -25
                                  -20
```

Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg -10 -5 Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro 10 His Pro Cys Ala Thr Tyr Pro Pro Xaa 25

<210> 450 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1

<400> 450 Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr -20 -15 Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro - 5 Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile 10 15 20 Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly 30 Phe Asp Leu Asp Met Asp His Thr Ile 40

<210> 451 <211> 54 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1 <400> 451

Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser -30 -25 Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser -10 Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys Ala Ile Ile Leu Met Lys 15



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<210> 452
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
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<210> 453 <211> 166 <212> PRT

 <400> 452

 Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala -35

 Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu -20

 Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg -5

 Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp 15

 Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln 30

 His Ser Pro Pro Lys Glu Xaa Leu Leu Leu Gly Ser Ser Ser Ala Gln Ala 45

 Ala Ile Gly Xaa His Leu Leu Leu Leu His Pro Cys Leu Asp Ile Pro Xaa 60

 Leu Pro Gly Xaa Pro Gly Pro Pro Lys

```
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                            -30
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                        -15
                                            -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
                                20
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
        30
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                                        70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                                    85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
                               100
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Lys Xaa Leu Trp Glu
        110
                            115
```



Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220>

<222> -26..-1

<221> SIGNAL

<400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -20 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg - 5 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 15 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 80 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 110 115 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 130 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 140 Arg Asn Trp Glu

<210> 455
<211> 91
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -64..-1

20

<210> 456

```
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Xaa
           -20
                                -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                    15
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                                50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                                        100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
                110
                                    115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
            125
                                130
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                            145
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                        160
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                    175
                                        180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
                190
                                    195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
           205
                                210
```

```
<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 457
Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro
-60 -55 -50 -45
```

Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa 220 225 230

Xaa



Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -35 Leu Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -20 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 25 30 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 125 Glu

<210> 458 <211> 107 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

<400> 458 Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg -25 -20 Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser -5 Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile 10 Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys 30 Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val 45 Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu 60 Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

<210> 459 <211> 121 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

```
<400> 459
Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr
            -10
Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr
                       10
Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys
                   25
                                      30
Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr
                                  45
Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg
                               60
Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg
                           75
Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln
                      90
Phe Leu Ile Pro Asn Leu Ala Leu Asn
        105
```

```
<210> 460
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 460
```

<210> 461

Met Lys Val Gly Val Leu Trp Leu Ile Ser Phe Phe Thr Phe Thr Asp
-15 -10 -5

Gly His Gly Gly Phe Leu Gly Val Ser Trp Cys Tyr Val Ser Tyr Leu
1 5 10 15

Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg Ile
20 25

```
<211> 109
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 461
Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys
          -10
                             -5
Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro
Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro
                 25
Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn
              40
Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His
                             60
Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser
                         75
Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala
```

90

95

```
<210> 462
<211> 143
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 462
Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala
                        -35
Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile
                    -20
                                         -15
Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu
                -5
Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp
                            15
Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu
                        30
                                             35
Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn
Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu
                                    65
Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr
            75
                                80
Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu
                            95
<210> 463
<211> 232
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 463
Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val
                    -25
                                         -20
Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa
                -10
Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu
Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu
                                            30
Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu
                    40
                                        45
Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser
```

60

Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly
70 75 80

Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys
85 90 95

Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
100
                       105
                                           110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
           120
                                       125
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
               135
                                   140
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
           150
                               155
                                                  160
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
                           170
                                           175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
                       185
Val Lys Cys Lys Phe Leu Tyr Asn
```

-20 -15 -10

Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
-5 - 10

Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
15 - 20 - 25

Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
30 - 35 - 40

<210> 466 <211> 215 <212> PRT <213> Homo sapiens

<220>



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<221> SIGNAL <222> -54..-1
```

<400> 466 Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -50 -45 Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu -30 Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -15 -10 Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 65 Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 80 85 Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu 100 Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 110 115 120 Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 130 135 Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 145

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<210> 468
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 468
```

Ile Ile Arg Lys Cys Phe Ile



•

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -43..-1
<400> 470
Met Thr Pro Gln Tyr Leu Pro His Gly Gly Lys Tyr Gln Val Leu Gly
                               -35
Asp Tyr Ser Leu Ala Val Val Phe Pro Leu His Phe Ser Asp Leu Ile
                           -20
                                               -15
Ser Val Leu Tyr Leu Ile Pro Lys Thr Leu Thr Thr Asn Thr Ala Val
                       -5
                                                           5
                                           1
Lys-His-Ser-Ile-Gln Lys-Asn-Cys-Met-Xaa-Leu-Val-Leu-Gly-Lys-Leu-----
               10
                                   15
Leu Ser Gln
```

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<210> 470 <211> 67



```
<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
                    -10
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                                10
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
                            25
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
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<220> <221> SIGNAL <222> -58..-1 <400> 472 Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His -55 -50 Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu -35 Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile -20 Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala - 5 Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly 15 Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile 30 Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa 45 Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser 60 65 His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro 75 80 Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys 90 95 Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly 105 Gln Val Asn

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<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
```

<222> -71..-1

120



```
<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
                        -65
                                            -60
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                    -50
                                        -45
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
                -35
                                    -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
                                -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
                            1-
                                            -5-
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                    15
                                        20
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
                                    35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                                50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
                            65
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
                    95
                                        100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
                110
                                    115
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
           125
                                130
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
                            145
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
                        160
```

```
<211> 178
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 474
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
      -35
                         -30
                                           -25
Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile
                     -15
                                        -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                                                . 10
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu
Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val
      30
                         35
Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn
Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
```

His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr

Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

70

65

<210> 474

```
60
```

```
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
110 115 120

Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
125 130 135

Ile Gly
140
```

```
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
                        -15
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                                20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
                           35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
                      50
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
```

```
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
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<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

225

<400> 478 Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 150 155 Ala-Tyr Pro Gly Asn The Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn



```
<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                        -15
                                            -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
            15
                                20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                            35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                       50
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                   65
                                        70
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
                                    85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                               100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
       110
                            115
Gly Lys Val Lys Ser Phe Lys
                        130
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                    -20
                                        -15
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
                -5
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                        30
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                    45
                                        50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
                60
                                    65
Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala
                                80
```

Gly Arg Gln Gln Lys Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa 95



```
Asn Asn Asn Arg Asp Leu Ser Met Val Arg Met Lys Ser Met Phe Ala
                       110
                                           115
Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe
                    125
                                       130
Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa
               140
                                   145
Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys
                               160
Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn
                           175
Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln
                      190
Ala Gly Gly Phe Leu Gly Pro Pro Pro Pro Ser Gly Lys Phe Ser
                   205
```

```
<210> 481
<211> 208
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -92..-1
<400> 481
Met Arg Glu Pro Glu
```

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -25 -20 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 40 45 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Ala 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro ______115_-

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<210> 482
<211> 86
<212> PRT
<213> Homo sapiens
```



```
<221> SIGNAL
<222> -39..-1
```

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -35 -30 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -20 -15 - 1.0 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 10 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 30 35

Arg Leu Leu Thr His Trp 45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220'>

<221> SIGNAL

<222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 -15 Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -5

Leu Ser Leu Arg Ser Ala Met Ser 10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

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<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly -10 - 5

Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 10

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 25

Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala 40

Thr

<210> 485

<211> 130

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<400> 485 Met Ala Met Trp Asn Arg Pro Xaa Xaa Leu Pro Gln Gln Pro Leu -50 -45 Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg -35 -30 -25 Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile -15 Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val 15 20 Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa 35 Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg 45 50 Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp 65 Ala Leu

<210> 486
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<400> 486

-80

75

-65 -60 Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly -45 -40 Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu -35 -30 -25 Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu -15 -10 Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr 1 5 Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His 50 Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa 70 Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 85 Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu

Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr

-75

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PCT/IB98/02122
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95
                            100
                                                 105
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
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                                            120
His
125
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<211> 36
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<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
        -15
                            -10
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                    5
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
                                    -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
                                -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
  5
                        10
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
       -50
                            -45
                                            -40
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
                        -30
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                    -15
                                        -10
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Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala

Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15 -10 -5 1
Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr
5 10 15

<211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -50..-1 Met His His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 -5 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln 40 Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

<210> 491



<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492

Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -10 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly 135 140 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 Ser Val Tyr Leu Gly Arg Ile Val 200

<210> 493 <211> 134 <212> PRT

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<213> Homo sapiens
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<220>

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<222> -19..-1

<400> 493

Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly -15 -10

Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr

Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala 15 20

Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile 35

Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro

Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg 70

Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu 85

Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly

Asp Glu Val Lys Lys Glu 110

<210> 494

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 494

Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly -10

Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn 10

Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly 25

Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr 40

Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His

His Arg Glu Gly Asp

<210> 495

<211> 292

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -29..-1



<400> 495 Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe -20 -25 Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr -10 - 5 Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr 10 15 Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr 25 30 Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu 40 45 Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn 60 Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val 90 Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile 110 105 Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser 120 125 Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu 135 140 145 Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe 155 Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu 170 175 Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe 185 190 Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg 200 205 Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro 220 215 225 Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg 235 240 Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg 245 250 Lys Lys Gln Glu 260

<210> 496

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -56..-1

<400> 496

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Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 30 35 Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 45 50 Ala His Pro Lys Val Leu Lys Val Ala Leu 60

<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -10 -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 498

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro -10 -5 Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 10 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 25 Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 40 45 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 60 Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu Leu Gly

Arg. Gln Leu 85

<210> 499 <211> 99 <212> PRT <213> Homo sapiens



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<220>
<221> SIGNAL
<222> -13..-1
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<400> 499

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro
-10 -5 1

Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 5 10 15

Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 20 25 30 35

Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 40 45 50

Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 55 60 65

Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly
70 75 80

Arg Gln Leu 85

<210> 500

<211> 108

<212> PRT

<213> Homo sapiens

<220>

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<222> -25..-1

<400> 500

Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
-25 -10 -10

Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys
-5 1 5

Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
10 15 20

Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 25 30 35

Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe 40 45 50 55

Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
60 65 70

Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
75 80

<210> 501

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 501

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -5 1

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu



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Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                            25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
                    55
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
                            105
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
    115
                        120
                                            125
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
                    135
                                        140
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
                150
                                   155
Thr Gly Gln Asp Phe Lys Glu
            165
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<210> 502
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<212> PRT
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<222> -15..-1
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Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
                    -10
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
Gln Gly Xaa Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                                            45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
                    55
                                        60
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Xaa Leu Thr Ser Glu Pro Leu
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<210> 503
<211> 183
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -57..-1
<400> 503
Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn
-55
-50
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Xaa Ala



Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 -30 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -20 -15 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn - 5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 1.0 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 95 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro

<210> 504 <211> 140 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -14..-1

<400> 504

Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -10 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 30 Leu Ser Met Pro Tyr Met Thr Arg Glu Gln Glu Arg Gly His Ala Ala 40 45 Leu Arg Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 55 60 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 105 Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr

<210> 505 <211> 59 <212> PRT <213> Homo sapiens

<220>

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<221> SIGNAL
<222> -14..-1
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<400> 505

Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His -10 -5

Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn 10 15

Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr 25

Gly His Met Arg Met Ala Ala Leu Leu Pro Gln

40

<210> 506

<211> 101

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -36..-1

<400> 506

Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg -35 -30

Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile -15 -10

Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg

Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys 20

Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly 35 40

Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa 50 55

Ala Ala Ser Xaa Gln

65

<210> 507

<211> 341

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 507

Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu ------50 -45

Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys

-35 -30 Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu -20 -15

Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg

20



Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn 30 Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp 65 Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe . 85 Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser 90 95 100 Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys 115 110 Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro 125 130 Tyr Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn 145 Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly 160 Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp 175 180 Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala 190 195 Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe 210 215 His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala 220 225 230 Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu 240 Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu 255 260 Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu 270 275 Ser Gly Ser Cys Leu

<210> 508 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 508 Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile -5 Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 10 15 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu

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<210> 509
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<212> PRT
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<221> SIGNAL
<222> -26..-1
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<210> 510 <211> 158

 Adoust 509

 Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys -25

 -25
 -20

 Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala -10

 Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser 10

 Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp 25

 Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu 40

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<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
               -40
                                  -35
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
           -25
                              -20
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                          -5
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
                  10
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
               25
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
                              45
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                          60
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
                      75
Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
85 --- 95
                                                      100
Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp Thr
               105
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<210> 511
<211> 130
<212> PRT
<213> Homo sapiens
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<220>
<221> SIGNAL
<222> -28..-1
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<400> 511 Met Asn Trp Glu Leu Leu Trp Leu Leu Val Leu Cys Ala Leu Leu -20 Leu Leu Leu Val Gln Leu Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu -5 Thr Leu Leu Trp Ala Glu Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu 10 Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu 30 Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser 40 45 Ala Arg Arg Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu 60 Asn Gly Asn Leu Lys Glu Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly

<210> 512 <211> 199 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -62..-1

<400> 512

Ile Trp

-55 Xaa Leu Ile Glu Leu Asn Tyr Leu Gly Thr Val Ser Leu Thr Lys Cys -40 -35 Val Leu Pro His Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val -25 -20 Asn Ser Ile Leu Gly Ile Ile Ser Val Pro Leu Ser Ile Gly Tyr Cys -10 -5 Ala Ser Lys His Ala Leu Arg Gly Phe Phe Asn Gly Leu Arg Thr Glu Leu Ala Thr Tyr Pro Gly Ile Ile Val Ser Asn Ile Cys Pro Gly Pro 25 Val Gln Ser Asn Ile Val Glu Asn Ser Leu Ala Gly Glu Val Thr Lys 40 45 Thr Ile Gly Asn Asn Gly Asn Gln Ser His Lys Met Thr Thr Ser Arg 60 Cys Val Arg Leu Met Leu Ile Ser Met Ala Asn Asp Leu Lys Glu Val 75 Trp Ile Ser Glu Gln Pro Phe Leu Leu Val Thr Tyr Leu Trp Gln Tyr 90 Met Pro Thr Trp Ala Trp Trp Ile Thr Asn Lys Met Gly Lys Lys Arg 105 110 Ile Glu Asn Phe Lys Ser Gly Val Asp Ala Xaa Ser Ser Tyr Phe Lys 120 125 Ile Phe Lys Thr Lys His Asp

135

Met Ser Gln Arg Ser Leu Cys Met Asp Thr Ser Leu Asp Val Tyr Arg

BNSDOCID: <WO 9931236A2>



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<210> 513
<211> 180
<212> PRT
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<222> -25..-1
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<210> 514 <211> 120 <212> PRT <213> Bos taurus

115

 A400> 514

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<212> DNA
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taacaggate teetettgea gtetgeagee caggaegetg attecageag egeettaceg
                                                                  120
cgcagcccga agattcacta tggtgaaaat cgccttcaat acccctaccg ccgtgcaaaa
                                                                  180
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